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THE FACTUAL BACKGROUND FOR THE TREATMENT OF PROGRESSIVE DEAFNESS FROM OTOSCLEROSIS*

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It is well to preface the presentation of any new or startling surgical procedures with a brief sketch of the factual background against which they must function. I shall now essay such an outline as I see it.

There are many theories and but few, if any, generally accepted opinions as to the etiology of otosclerosis, although the literature on the bone pathology and pathological anatomy is extensive; probably no other cubic millimeter in the human body, certainly no part of the skeleton, has been more extensively explored. In spite of this, we not only are ignorant of the etiology of the peculiar bony changes in the labyrinthine wall, but also of what causes them to cease in various stages of development coincidental with, because of, or in spite of treatment.

The mere fact that bone is involved implicates some abnormal local or general blood or lymph changes, probably in the calcium, phosphorus, or phosphatase, dependent on, caused by, or coincidental with, local circulatory impedences. It may be that the pathogenesis of clinical otosclerosis (ankylosis of the stapes) is predicated upon the prior impedence, or interference with free motion in the labyrinthine windows, due to residues from past inflammatory episodes, supplemented or not by other factors. Such impedence, by interfering with the normal movements of the annular ligament and round window membrane, would alter the local pressure, blood volume and nutrition, the local pH and CO_2; and in the presence of a

* Delivered before the Section of Otolaryngology of The New York Academy of Medicine, October 6, 1937.

predilection for—or the actual presence of—a nearby otosclerosis or other bone dyscrasia, would accentuate and give direction to these local conditions, and thus increase the already abnormal states. It is my opinion that the circulation and therefore the normal nutrition of the areas of predilection for otosclerosis are affected by any long continued diminution of motion in the membranes of the oval and round windows, and that any change in the circulation to establish a new vascular adjustment is in itself a potential threat to normal osteo-metabolism. These suggestions are made more attractive by the fact that although one out of twenty adult autopsies disclose the presence of otosclerosis, less than a quarter of these show symptoms of impedence in the labyrinth windows. If more carefully examined, I am sure a larger percentage would show defective hearing, but, even so, it is clear that otosclerosis does not always cause deafness.

There is no convincing evidence that any medical or surgical treatment has ever resolved or removed the lesion of established otosclerosis. There is no way to safely remobilize the stapes, or the oval and round window membranes, once any of these become calcified and immovable in their windows in the labyrinthine wall, and therefore there remain but two possible means to thwart the process. The first is to stop the lesion by medical or surgical treatment before deafness occurs. The second is to circumvent the lesion by surgical techniques; to open a new sound channel into the labyrinth; to reestablish, for sounds received through the air, two movable ports —one for the reception and one for the release of the sound pressure vibrations—so that the basilar membrane can function more normally. If the oval and round windows are both completely ossified, it will be necessary to construct two new ports into the labyrinth, one into each scala. If only the oval window is ossified, it will be necessary to construct but one port into the labyrinth and this must be made into some portion which connects with the membranous ducts leading to the scala vestibuli. For sounds received through the cranial bones only one port

is necessary for perfect hearing, because the pressures are received by the labyrinthine fluids through the squeeze of the cochlea wall. No second open port of entry is necessary.

The diagnosis of even uncomplicated otosclerosis is not always easy, and the diagnosis of otosclerosis complicated by other lesions, as it generally is, is often very difficult, but a careful otologic examination will give a correct answer in eight out of ten instances after deafness has been detected. There is no sure way of making a diagnosis except at autopsy.

A greater and unsurmountable difficulty has always been the lack of any means of detecting otosclerosis before deafness comes on. If this could be done, it would be possible to subject each patient to treatment, and a preventive or corrective method of choice would in time evolve. I have recently reported some clinical experiments which suggest a logical approach to this problem, and which give some promise of a successful solution.*

The failure to discover abnormalities in the blood and tissue juices of otosclerotics does not mean that abnormalities have not been present. It may mean that they are too small or variable to be detected by the means now available, or that our search has been instituted so long after the cause has disappeared that all signs of their presence have been removed or become masked by subsequent lesions. In any event, in established otosclerosis the blood and tissues, other than the lesion itself, appear to be similar to those in otherwise healthy persons.†

Methods for overcoming these defects in clinical and laboratory research have been suggested, but all are difficult to put into operation. One measure I am advocating as a routine is that all otosclerotic families submit their children to careful and regularly repeated examinations, preferably some years before the critical ages for the onset

* E.P.F. A Method for the Early Detection of Otosclerosis. A Study of Sounds Well Above Threshold. *Archives of Otolaryngology*, Vol. 24, pp. 731-741, December, 1936.

† Fowler, E. P. Calcium, Phosphorus and Cholesterol in Otosclerosis *Arch. Otol.*, Jan., 1931, Vol. 13, p. 77-83. *Trans. Am. Otol. Soc.*, 1930.

of otosclerosis, that is to say, some time before deafness from otosclerosis is most frequently recognized, and several years before puberty, child bearing and the menopause. There is no other way to clinically study or diagnose early otosclerosis and there is no better time to institute a study of preventive measures.

Because of the fact that the hearing of those suffering from otosclerotic deafness, like the hearing of other humans, varies from day to day, from hour to hour, and even from minute to minute, with the weather, the attention and mental states, and with changes in other lesions and conditions coincidental with or contributory to the otosclerosis, many treatments and so-called cures have been given credit for beneficial effects on the otosclerosis. *None of these have diminished the otosclerosis or the deafness caused by the otosclerosis.* This does not mean that proper treatment cannot improve the hearing in spite of the permanence of the bony lesion; because as I have shown, otosclerosis is more regularly accompanied by other lesions contributing to the deafness than is realized, and some of these lesions are amenable to treatment.* The otologist should do his utmost to discover and diagnose these lesions and utilize every device useful for their amelioration. He should not delude himself or his patients by believing that such improvements have been due to any effect on the otosclerosis. He should not by catheterization and over inflation, by so-called finger surgery of the Eustachian tube, or in any other way injure the patient. Many otosclerotics show stretched drums, extensive scars and adhesions from practices such as these. Their condition has been made worse by unwarranted and unscientific treatments.

In addition to, or in the absence of non-surgical treatment, hearing aids and lip reading are of great service, and imperative if the deafness becomes marked for speech (over 40 db. loss), but many people are so deaf that no hearing device is of much service, and these people have in the past had no hope of ever hearing again.

* Fowler, E. P. Otosclerosis Complicated by Other Lesions. *Annals of Otol., Rhin. & Laryn.*, Sept., 1933, Vol. 42, No. 3, p. 714.

Recently this picture of hopelessness has been changed. There is in process of development an operative procedure which has proved successful in certain selected cases of otosclerosis. The deafened have been actually made to hear again. A seeming miracle has taken place, but, as scientists, we must proceed cautiously with these new operative procedures, because they have not been generally accepted as satisfactory. In fact, they are not always satisfactory. In unskilled hands they may prove useless, very distressing, or dangerous. This is particularly true of the intracranial techniques. They may destroy even the little hearing the patient possessed. They may destroy life.

There is no reason to believe that these operations can directly lessen nerve deafness, but I have observed cases showing marked loss of bone conduction (the usually accepted criterion of neural lesions) and very severe deafness from otosclerosis which may be greatly benefited, because these are the cases with both the oval and the round windows completely ossified.* These are the cases that often say they are totally deaf; they believe they cannot hear anything before operation and may think they hear perfectly after operation. They do not hear perfectly. They do hear much more than they did before.

Deafened people are so anxious to grasp at any hope of relief and so insistent that something drastic be done that it is sometimes difficult for the surgeon to dissuade them, even though operation is not indicated. This, however, he must often do.

There is no doubt in my mind that in a large proportion of cases properly selected and treated, many people have experienced marked improvement from these operations for various lengths of time.

One of the chief obstacles to the acceptance of the operative procedures has been the use of functional hearing tests of doubtful accuracy or completeness, by air conduction and bone conduction. There has been doubt as to just how much change has taken place because of the opera-

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of otosclerosis, that is to say, some time before deafness from otosclerosis is most frequently recognized, and several years before puberty, child bearing and the menopause. There is no other way to clinically study or diagnose early otosclerosis and there is no better time to institute a study of preventive measures.

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tion; just how much the improvement is due to the mechanical effects of the operation and how much to the psychological effects of the operation. The carrying out of accurate hearing tests is complicated by the fact that in marked binaural obstructive deafnesss it is difficult to avoid crossed audition both for the test frequencies and for the noise used to mask the opposite ear. It is often difficult to eliminate the hearing of the opposite ear and yet obtain a true picture of the hearing in the ear being tested. For any improvement in the hearing to be convincing, all these difficulties must have been kept in mind and largely overcome in the methods used both before the operations and at various periods following the operations.

One of the pioneers in the surgical methods for lessening the deafness of otosclerosis is Prof. Maurice Sourdille, of Nantes, France. For twelve or thirteen years he has persisted and finally perfected his techniques in middle ear and labyrinthine surgery to a point where he feels warranted in making certain definite announcemnts. Dr. Sourdille after serving as interne and then resident in surgery and as assistant to the otolaryngologist, Dr. Lermoyez, saw four years of service in the World War as the head of a surgical unit in the army of France. He was awarded the Croix de Guerre. In The New York Academy of Medicine library may be found practically all the contributions of Dr. Sourdille, beginning with a thesis on "Aural Surgery" written in 1914-15, and a volume on "War Otitis" and "War Deafness," written in collaboration with Dr. Bourgeois, otorhinolaryngologist to the Paris hospitals. This was translated into English by J. Dundas Grant. In 1926, becoming interested in Bárány's research on the semi-circular canals of dogs, and Holmgren's clinical application of Bárány's findings, he attempted to verify clinically and amplify the results of these experimentors. Slowly a new surgical technique was evolved and the successive developments published in the medical press of Europe and America. Recently an extensive monograph was published on his chosen subject.

NEW TECHNIQUE IN THE SURGICAL TREATMENT OF SEVERE AND PROGRESSIVE DEAFNESS FROM OTOSCLEROSIS*

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In beginning this address, I should like first of all to express my gratitude to Dr. Fowler for the honor of being asked by him to give you my opinion on one of the most difficult and arduous problems in our specialty. I should also like to express to him, and all of you, who saw service in France, my great appreciation for the sympathy that was shown to the Country to which you came to succour in a time of great distress. You abandoned your firesides, your occupations and your interests; that is a thing which a Frenchman cannot forget, and that he likes to recall.

I wish also associated with this great honor to me, the names of some of the masters to whom I am indebted for what I have been able to do: Lermoyez and Henri Bourgeois, of Paris, for general culture, and to Professors Bárány of Upsala and Gunar Holmgren of Stockholm for the particular question that brings us together tonight: The surgical treatment of otosclerosis.

I regret very much not having enough command of your language to go as much into the details as I should like to in discussing such a subject. I am sure you will excuse the way my subject is presented and take away only the point of what is said, not how it is said.

The surgical treatment of otosclerosis, begun twenty-five years ago by Professor Bárány, Doctor Jenkins and Professor Holmgren, has received in the past ten years such an impetus that it has become one of the most captivating subjects in contemporary otology, but also one of the most complex. It is not possible to treat it completely in a few moments. Besides, the late Dr. Duel and Dr.

* Delivered before the Section of Otolaryngology of The New York Academy of Medicine, October 6, 1937.

Fowler have set forth the general state of the whole question in the recently published third volume on otosclerosis. I wish therefore, this evening, after a rapid tour of the horizons, to show you more particularly my personal experiences, what seems to me to be to the point—what it is already possible to do.

In a general way, it is possible to group the operative procedures by various authors, who have tackled this question, into two large groups. The first comprises the procedures which have been inspired by the presumed pathogenesis of otosclerosis. They propose to attack the disease at its root and the operations are performed outside of, or even far from the ear. These are:

1. The operation of Wittmaack-Heyninz-Rollin, designed to combat the perilabyrinthine venous stasis. This operation may be called "elevation of the supra-tympanic dura mater." I hope that Dr. Fowler, Jr., who has just returned from Hamburg, will tell you something about it later.

2. The operation of Alonso-Chiarino, which consists in removing one parathyroid or suppressing its function by ligature of its principal vessels. The operation is recent and we cannot yet judge the results.

In every way these operations with a pathogenetic inspiration are designed with one purpose in mind: the arresting of the progress of the disease. But, supposing this final purpose obtained, it is not wholly a question of making the disease retrocede, nor of recovering a too deficient audition. They are therefore indicated only at the very beginning of the sickness and once the cases have passed the early stages, they should be put in the second category.

The second class of operation, comprising those which are properly auricular, attack the local functional troubles. They are based on the acoustic results produced by fenestration of the labyrinth. These are by far the most numerous. They are the newest and most fertile and give promise of being a definite triumph. It is these which I shall discuss for the rest of this conference.

I. Operations Based on Fenestration of the Labyrinth

Historical.

With what we know today, it is easy to understand why the first tentative surgical procedures which took place in the last century could not succeed—in particular those used towards 1890, the extraction of the stapes or the operation of Kessel. Here are two cases of the common lesions of otosclerosis. The footplate of the stapes is so fixed by an osseous process and its crura so wedged in by the borders of the deformed oval window that extraction of the ossicle is practically impossible. If one exerts traction on the crura they are certain to be fractured and there is no other way of raising the footplate. Besides, be assured that even if this could be done, the large communication established between the hole opened by the ablatum of the tympanus and the labyrinth will permit infection to enter and will thus lead to inevitable total deafness. It was this simple conception which led in 1900 to an official condemnation of the operation which was so severe that we are still influenced by it.

When Bárány, in 1910, proposed the opening of the posterior semi-circular canal he had a double purpose:

1. Acoustic: to create a labyrinthine window which would compensate for the suppressed resonant waves, from which he hoped that the round window would then take over the function of the non-utilizable oval window.

2. Surgical: to avoid the opening of the mastoid cells and so avoid the mastoid infection and the secondary labyrinthitis, so much to be feared.

An immediate result was obtained: the return of audition on the operating table; but the result was ephemeral; for, a few days after the operation, the increase in hearing disappeared.

Doctor Jenkins and Professor Holmgren in opening the external and superior semi-circular canals had the same experience.

Since the gain in hearing appeared with the opening of the labyrinth, one can easily deduce that its disappearance

was due to a bony closure of the labyrinthine fistula. For fifteen years these authors tried to combat this bony closure of the fistula; they tried soft tissue; they used fat grafts. They used connective tissue grafts with and without prostheses. They used gutta percha.

On the other hand, each of these surgical procedures was attended by more or less complete or conservative radical operations. There was the greatest chance of a surrounding infection, extremely difficult to control, and often connecting with the labyrinth so as to destroy it.

So Bárány and Holmgren adopted the mastoid operation without opening of the external auditory meatus and with immediate closure of the retro-auricular wound.

When, in October 1924, I was introduced to this type of surgery by Prof. Holmgren, I quickly saw that there were two problems to be attacked: the acoustic and the surgical. But if the solution of the two problems was indispensable to obtain a result, the order of the researches was not an indifferent matter. I believe that in order to solve the acoustic problem, it was necessary to determine the mechanism of the return of hearing as well as finding the way of conserving it. The surgical problems would naturally follow and adapt themselves to the physiological conditions required. Experimentation has finally proved that there was a concordance with the pathological problem.

On these bases I created surgical procedures which I named "tympano-labyrinthopexy". They consist in associating the opening of the external semi-circular canal to the new tympanic system derived from the normal system. For the last ten years I have remained faithful to this principle; all my efforts, with the collaboration of my Assistant, Dr. André Loué, have been bent towards the realization of its technique. Two of my friends, Doctor Ledoux of Brussells and Dr. Tato of Buenos Aires, have been kind enough to follow me in this path. More recently, in 1936, Professor Holmgren has brought an important modification in his procedures, on the principle of his en-

domastoid operation, consisting in the simultaneous opening of two or three semi-circular canals and the application of a gold leaf between the labyrinthine fistula and the membranous cover.

In order to judge the value of these different procedures, let us study more in detail the problems to which they give birth.

II. The Acoustic Problem

A. *The mechanism of the return of hearing at the moment of the opening of the labyrinth*

From the opening of the semi-circular canal, that is, the perilymphatic space, *there is an outflow of perilymph.* Presently, but only after the passing of a moment, the hearing increases. Why? Professor Holmgren has said, "it is the decompression which does this," but what does he mean by that? Since the semi-circular canals are at different levels, on opening them, all the spaces above the level of the labyrinthine fistula *become empty.* Of course, the pressure is diminished. But in my opinion there is something else much more important. There is formed in the labyrinth *a free surface of perilymph.* The mobilization of this perilymph is therefore considerably augmented under the influence of a sound wave at the level of the opening of the labyrinth, not only by air conduction but also by bone conduction from the entire cranial vault.

It is then the *half-emptiness* of the perilymphatic space with the resultant very great mobility of the perilymph which is the cause of the increase in hearing. This is what I called at Norwich, England, *"the mechanism of the half-filled flask."*

It is in fact easy to reproduce this phenomenon with the aid of two flasks placed upon a table. One is full of water with its cork indicator submerged, and closed by a cork. The other is half full, but with the same cork indicator. The least shock given to the table puts the indicator of the half filled flask in vibration, while that of the completely filled flask rests immobile.

How is sound energy transmitted to the perilymph? At the same time, both by the direct influence on perilymph at the level of the labyrinthine fistula which is exposed to the exterior air and by bone conduction from

the cranium. Because it is manifest that if the labyrinth being open, on suturing the posterior mastoid wound and on closing the external auditory meatus with wax or paraffin, the auditory gain is diminished but the hearing still remains better than it was before the creation of the labyrinthine fistula. Also in the first hours that follow the opening of the labyrinth, the Weber is often lateralized to the side of the open labyrinth which indicates that the bone conduction has been increased on that side.

This mobility of the perilymph is still greater in the case of multiple simultaneous opening of either two, or even three semi-circular canals, as has been recently performed by Professor Holmgren. He has stated that at each new opening of a canal there is a corresponding increase in hearing which permits the patient to hear ten, fifteen or twenty times the distance that he could hear before the operation.

B. *Mechanism for the conservation of the improved hearing*

The first idea which comes to mind will be to conserve indefinitely this state of semi-vacuity of the labyrinth. But for that, it would be necessary to produce a *continual outflow* of perilymph in a quantity just equal to its relatively rapid rate of secretion.

Practically, the least membrane that one places on the labyrinthine fistula — a piece of connective tissue — the slightest clot of blood adheres rapidly to the bony edges and prevents the escape of the perilymph. The *labyrinth refills,* the pressure increases and the mobility of the perilymph diminishes; so does the increase in hearing. While the membrane over the opening remains thin, supple and easily depressable, the hearing continues to remain considerably increased; if this membrane becomes thickened or ossified, all the gain disappears.

But experience has shown that even with a refilled labyrinth *it is still possible to produce hearing by mobilizing the perilymph of this refilled labyrinth.* We are going to see how.

III. The Surgical Problem

The surgical problem presents itself under two headings:

1. By what mechanism can the mobilization of the perilymph be conserved in a durable way?

2. Can this hearing mechanism be practically produced surgically?

Hearing mechanism

a. *The continual escape of perilymph* seems to have been produced recently by Holmgren who placed a piece of gold foil over the labyrinthine fistula. The gold foil prevented the adherence of a fat graft to bony edges of fistula. Between the gold foil and the bone the perilymph could filter out. Evidently the adherence of the fat graft to the edges of the gold foil puts off the problem rather than solves it.

b. *The direct mobilization of the perilymph of a filled labyrinth* is possible. It is sufficient to place on the labyrinthine fistula, either directly or else with interposition of thin cushions of fat or connective tissue, a prosthesis of a certain weight, a foreign body such as a piece of gutta percha (Bárány, Holmgren). These masses in contact with the bony walls of the mastoid receive sound vibrations by bone conduction and are displaced by them. This movement induced at the level of the labyrinthine fistula produces little shocks which hit the perilymph and set it in motion. This is what I have called *the mechanism of the bell.*

c. *The indirect mobilization of the perilymph in a filled labyrinth can be produced by mobilization of the membrane covering the labyrinthine fistula by means of a reconstructed tympanic system.* This is the method which I have personally devised and have been using for the past ten years. I have given it the name "tympano-labyrinthopexy." It consists in joining the covering membranes of the labyrinthine fistula with the superior border of the membrana tympani whose excursions have been increased by the resection of the head of the malleus.

The incus preserved in its high position plays the rôle of a mobile prop and permits the displacement *en masse* of the entire system. The proof that this is the correct interpretation lies in the fact that immobilization of the incus or adherence of the flap between the drum and the labyrinthine fistula no longer permits the conservation of the hearing, which has been observed to be increased at the

operating table. I have tried to demonstrate this with a stroboscope. So far I have had no success, however.

IV. Surgical Results of These Diverse Procedures

A. In the two first procedures, utilizing the gold foil and prosthesis with gutta percha, the operation can be done simply enough in one sitting by the *endo-mastoid route* with immediate closure of the post-auricular wound. One thus avoids the danger of infection and recovery can be rapid, normally fifteen or twenty days. But against these advantages of which the most evident is the speed of recovery, one must put these inconveniences.

1. What is the value of the surgical result for this type of auditory mechanism?

I believe that I can truthfully say that the essential purpose of the prosthesis has always been, in the words of its authors, to prevent the closure of the bony fistula. Their action I believe to be very feeble. Actually the closure of the fistula is easier in these cases than without prosthesis.

I have already explained that actually the rôle of the prosthesis is not to keep the fistula open but to produce an auditory mechanism of its own. Unhappily this is the weak point of the procedure. The mechanism is artificial and very delicate. The secondary immobilization of the prosthesis or its isolation from bone by masses of granulation tissue, connective tissue grafts, or fibrous tissue, often supervenes and destroys rather rapidly its good effects.

2. After the mastoid wound is closed we no longer have any external control of the labyrinthine fistula or of the function of the prosthesis. If re-intervention is necessary, it must be done blindly and whatever modification or retouching is done, the same conditions return and again there is no progress.

3. Finally there remains the great uncertainty of the tolerance for a foreign body of an exact weight and an exact surface placed in contact with bone at the bottom

of a mastoid susceptible to direct infection in the course of the operation or later by way of the Eustachian tube and middle ear.

Besides, even in fracture repairs such foreign bodies produce such serious accidents that secondary ablations of them are often necessary. There are those who believe a foreign body may increase the susceptibility to infection of the labyrinth and through the labyrinth the meninges.

B. The tympano-labyrinthopexy has against it its complicated appearance and the difficulties of its realization.

Against it is to be noted:

1. It cannot be done in a single operation. It is necessary to have two or, better, three successive operations and frequently the third stage must be repeated in order to obtain a permanent labyrinthine fistula with a maximum effect.

2. It is an *extra-mastoid* operation, that is to say, it puts the interior of the mastoid cavity in communication with the cavity of the external auditory canal and so makes it susceptible to an external otitis. It is necessary to accept this risk, but at a moment when there is no danger to the labyrinth, with careful aseptic technique, this stumbling block can usually be avoided and in any case can be surmounted before the opening of the labyrinth.

Of its advantages we can say:

1. In case the transformation of the tympanic system is successfully carried out, its function is definitely assured without the possible variation of the type seen with the prosthesis.

2. The tympanic system and the labyrinthine fistula are constantly in sight and can be tested with a manometer or any other imaginable apparatus of control. This is very important.

3. With the tympano-labyrinthopexy, the opening of a *single canal* (the horizontal, the most easy of access) produces a considerable amelioriation of the auditory malfunction, from forty to fifty times or more the distance of the preoperative hearing. With the prosthesis procedures,

in order to get the best results it is necessary to open several semi-circular canals. This is one of the greatest objections that one could possibly make to operations in this category. Wounding of the membranous canal is one of the greatest dangers that one faces in the curing of deafness. The more osseous canals that are opened, the more the risk of injuring the membranous canals. It is better to concentrate on the less delicate manoeuvres on the tympanic system than on the labyrinth, which is so very fragile.

4. Biologically it is unnecessary to add any foreign body to the organism with the consequent danger of intolerance, or of labyrinthine suppuration and its propagation to the meninges.

5. Each difficulty is attacked separately and the results proved before passing to the next.

6. Touching up the operation is easy and is directed exactly at the point at fault. Most often it is the labyrinthine fistula which is closed by an osseous callus. Now the formation of this callus is the result of two elements: the ossification of the endosteum and the proliferation of the osseous surface. Practically it is very difficult in a single opening to raise the endosteum completely and prevent proliferation of the osseous surface. But if one lifts up this new-formed osseous lamella, one elevates at the same time both the ossified endosteum, and the osseous surface, cut in the callus, has less tendency to proliferate. Experience has shown that in most cases, the results are definite after this second opening of the labyrinth.

It is because of these advantages that I remain constantly faithful to this procedure, the nearest approach to the natural mechanisms of hearing. I prefer to adopt the most normal, the most sure and the least dangerous mechanisms, whatever the difficulties, even if certain material inconveniences have to be borne, to which conditions the surgical technique must submit. The three primary considerations are the safety of the patients, the regularity, and the quality of the end-results.

V. The Pathologic Problem

It is now an undeniably observed fact that a local surgical treatment is sufficient to re-establish hearing and to conserve it without change for several years, as long as the necessary conditions expressed above are adhered to. Doubts expressed on the durability of the results and the cessation of the evolution of the disease are no longer valid after eight years of observation.

How then can we make these results accord with the diverse known pathologic conceptions which are still in favor? Far be it from me to think of minimizing the importance of these histologic considerations. But alone they do not constitute the whole malady. There are perhaps elements that the microscope cannot show. It is necessary also, according to the ideas of Professor Leriche, to use the aids of clinical and operative physiology. Tympano-labyrinthopexy permits this being done.

It seems well established that the known osseous lesions do not act directly on the auditory elements but probably through the intermediary of the liquid media of the ear, in particular modifications of the perilymph.

Objectively any durable and permanent decompression of the perilymph suffices to arrest the progression of the deafness. What difference does the method make if the functional result is obtained? In our uncertainty, nothing can prevail against undeniably observed facts. But in order to improve the hearing, something more is necessary to reestablish the mobility of the perilymph by one of the described mechanisms.

In the present state of our knowledge, at least of mine, the procedures most direct and best worked out, and the one on which we have the most experimental data, is tympano-labyrinthopexy: the reconstruction of a secondary tympanic system associated to one labyrinthine fenestra. These two structures complete each other and are inseparable.

Operative Indications

Here it is necessary to consider three groups of facts: (1) *Nature and degree of the deafness;* (2) *Indications of primary otospongiosis,* hereditary or not, without middle ear inflammation but with fixation of the stapes which is diagnosed by the following acoustic methods: (a) raising of the lower tone limit from 32 to 128 double vibrations; (b) Rinne negative; (c) Schwabach prolonged; (d) Conservation of a certain degree of labyrinthine sensibility manifested by an audition consisting of between 50 cm. of whispered voice and 50 cm. of shouted voice with the opposite ear masked during the testing of the shouted voice.

Absolute deafness, or almost absolute, ought to be considered a contra-indication if one is going to conserve for this operative procedure its demonstrative value. However, I have found in some of these cases 30 to 40 cm. or perhaps one meter audition for the loud voice on opening of the labyrinth, particularly in young subjects, and when the bone conduction values are below normal. But if the Schwabach is much diminished there can be no perception of sound. In the first case, the advantage is considerable since the patient can again converse directly for short distances and indirectly, with a hearing aid for considerable distances. One should therefore not exclude these patients from a chance of recovery. They would choose it themselves.

CONTRA-INDICATIONS

1. *Local Anatomical Indications*

External auditory meatus wide and straight. Middle ear of large dimensions, well vascularized and resistant.

Medium pneumatization of the mastoid and preferably the wall of the zygoma should not pass beyond a vertical plane through the posterior border of the condyle of the mandible.

2. *Secondary Otospongiosis*

That is to say, progressive deafness with the same acoustic formulae that has been accompanied by inflammatory

alterations in the middle ear, either recently or in the past, characterized by redness of the drum or the handle of the malleus, deformation of the membrane, heavy adhesions, old or recent perforations, open or closed by a thin cicatrix. The inflammatory element starts up again after section of the head of the malleus, the lesions on the articular surfaces of the cartilage of the incus which necessitates the secondary ablation of this ossicle. Any damage of the tympanic substance or cicatrix can destroy the internal plastic flap with subsequent suppuration and necrosis of the incus.

3. *Poor General Health and Unsuitable Ages*

One can operate on patients between eighteen and fifty-five years of age. Younger patients are hard to manage and operation under local anesthesia is rendered impossible, as well as the postoperative dressing, by the turbulence and incooperation of the patient. Patients over the age of fifty-five tolerate the necessary analgesics and hemostats such as morphine, scopolamine, ephedrine, adrenalin with difficulty. Cardiovascular disorders are exacerbated by opening the labyrinth. But even before the age of fifty-five, obesity, alcoholism, cardiovascular, pulmonary, hepatic or renal afflictions are all absolute contra-indications for this type of surgery. All candidates for the operation should have a general complete physical and clinical examination.

4. *Local Anatomical Contra-Indications*

Narrow external auditory meatus—a crooked or flattened meatus. The length of the flap will be insufficient to close the attic and the aditus with subsequent danger of infection and suppuration of the middle ear.

Too extensive pneumatization of the mastoid, of the squamous portion of the temporal bone and especially of the root of the zygomata. All these cells must be opened and scraped of this epithelium to avoid secondary suppuration or one will have considerable bony destruction.

It is absolutely necessary before deciding on an intervention to take a stereoscopic radiogram of the ear in question and to interpret the films correctly. For the last two years all my patients have been systematically X-rayed stereoscopically by Doctors Dano and Lainè. Their precise technique has furnished very interesting radiograms and has permitted me to fix the operative indications with exactitude.

Operative Technique

Tympano-labyrinthopexy is performed in three principal stages separated by intervals of about four or five months.

The first two stages are devoted to the transformation of the tympanic system and the thorough modifications of the mastoid region.

The third stage consists in the establishment of the labyrinthine fistula at the level of the new tympanic system.

The operation is conducted in the following fashion:

First Stage:

This is performed entirely within the external canal. It consists of lifting the soft parts, thick cutaneous soft parts, fibrous bands and periosteum of the posterosuperior demi-circumference of two-thirds of the external auditory meatus. This is done through a postauricular incision or even by the external auditory meatus if it is sufficiently wide.

The post-operative care consists in obtaining on the surface from which the periosteum has been removed, a supple cicatrix, but resistant, without sebaceous glands. It takes six or eight weeks for this cicatrization to be complete.

Second Stage:

This is done almost entirely in the middle ear, making an incision through the previous post-auricular scar. One first separates the thin cicatrix made at the first operation from the post-superior canal wall. This cicatrix consists of new skin and scar tissue as well as the upper border of the drum. I have given it the name "internal plastic."

Then one resects the mastoid, opens the aditus and attic so as completely to exenterate the cell structure and show up the body of the incus and the head of the malleus. The joint which joins these two bones is opened and the two ossicles separated. Using a specially constructed snare, the head of the malleus is resected, care being taken not to puncture the membrana tympani or displace the incus, which should stay in high position and conserve its posterior and inferior articulations. The internal plastic (prepared flap) is then elevated and its bleeding surface applied to the incus, its internal surface to the attic, the aditus and even the antrum. The middle ear is thus hermetically sealed in its superior portion. One ends by covering the lower part of the mastoid with an external plastic made up of scraps of skin and muscle elevated from the inferior surface of the mastoid.

When, after epidermatization of the operative cavity (which in such cases as in wounds of radical operation usually takes six or eight weeks) one examines the transformed ear through the external auditory meatus, one finds that the external canal is considerably increased in size and communicates directly with the mastoid cavity. This large vestibule communicates *behind* on the curve of the horizontal semi-circular canal covered with a more or less thin cicatricial pedicle in front. It communicates with the modified tympanic system consisting now of the drum and the internal plastic which is continuous with its superior half circumference. This internal plastic over the incus, mobile on its posterior and inferior supports, ends on the surface of the horizontal semi-circular canal, which is just below and behind the incus.

Third or Labyrinthine Stage:

This consists in lifting up the endo-mastoid flap at the level of the external semi-circular canal, which is opened with great caution, so as not to injure the membranous canal. As soon as this opening is obtained, the increase in hearing seems considerable, ten, twenty times and even

more the pre-operative hearing distance. The cicatricial endomastoid flap produced at this level is put in place, consisting of the internal plastic, lowered from the superior border of the incus, which will from now on cover the labyrinthine fistula.

The hearing which ordinarily decreases in the days following the operation, increases as soon as cicatrization has taken place, and attains or even surpasses the hearing observed on the operating table, the moment the labyrinth is opened. It is now easy to observe with a manometer that a feeble air-pressure—from 2 to 10 cm. of water—in the external ear, determines a very definite horizontal nystagmus; at the same time the patient feels a more or less intense sensation of vertigo. Furthermore, one can observe with the tuning-fork the return of aerial hearing of low sounds (64 and even 32 double vibrations); the Weber is changed, lateralized from now on to the non-operated side, and the Rinne can become positive on the operated side while it remains negative on the opposite side.

In a great number of cases, unfortunately, the success is ephemeral: four, six, or ten weeks later, one sees the aerial hearing diminish, the Rinne becomes negative and the Weber indifferent. At the same time, the air pressure in the meatus can attain 40 and even 60 cm. of water without determining nystagmus, nor a sensation of vertigo. This is due to the fact that the labyrinthine fistula closes, due to the reconstitution of a rigid bony layer, which rarely attains the thickness of the primitive bony wall of the canal, and more often does not exceed a few tenths of a millimeter. It suffices, in a complementary operation, to extract this bony film, to see the hearing gain of the first operation return, and sometimes be even greatly increased. This time the result will be lasting, the regenerating process of the bone becoming gradually exhausted. In many cases, however, I had to open the labyrinth three times.

RESULTS

In 1935, at the time I published my Report to the Congress of Paris, my statistics were as follows:

Patients operated on.....	109
Number of operations performed..	325
Positive results	74 per cent
Composed as follows:	
Very good results, that is to say, ten times and more previous hearing distance	40 per cent
Good results, five to ten times previous hearing distance.....	14 per cent
Mediocre results, from two to five times previous hearing distance..	20 per cent
Fatalities	None
The number of patients now treated or under treatment exceeds.....	140
And the number of operations....	400

By utilizing my technique, the second method which I have just discussed, and a differential snare for the section of the head of the malleus (a happy modification of my previous snare created by one of my patients, barrister-at-law de Rienzi) I am now able to attain 80 per cent positive results, of which 60 per cent are superior by ten times to the pre-operative hearing distance.

I have had in mind, foremost, the creation of a surgical technique giving very important practical hearing results, and creating an impression on the patient and his immediate relations, but I hope that in the future a precise audiometric measurement will permit us further to improve the method and, especially, its indications and contra-indications.

CONCLUSIONS

The tympano-labyrinthopexy permits us to obtain, in cases of deafness from otosclerosis, a fearful and frequent disease, lasting results unknown up to the present time and absolutely comparable to those obtained in ophthal-

mology, in cataract and glaucoma. But, just as for cataract, before the intracapsular extraction of Barraquer, two operations were most often necessary, even so, in otosclerosis, one must, in the majority of cases open the labyrinth twice in order to obtain lasting results. We must still work to solve this problem of osteo-genesis, which will diminish not only the unpleasantness of re-opening the labyrinth, but one of the causes of grave failure: the injury of the membranous canal.

But must we, as long as we have not attained this result, consider this operative procedure as still being in an experimental period, and of an exceptional application? I do not believe so. During more than half a century, cataracts were operated by a two-stage method, before the extraction in a single stage operation. The case must be likewise in otosclerosis, as it is well worth doing a complementary operation rather than to leave the labyrinth irremediably impaired, inasmuch as, the greater the deafness, the poorer the results.

The tympano-labyrinthopexy is today a precise operation, the fundamental elements of which seem definite—that is, the decompression of the labyrinth and the reconstitution of a tympanic system. Personally, I have done these operations for years, I can say daily, at my Private Hospitals in Nantes. But we still have a great deal of work to do to adapt our theories to these first results, and to solve the new problems to which they give birth.

Gentlemen, I would like to be able to convince you that the moment has come to give to this surgical therapy a very large diffusion, because the number of patients who require this treatment is considerable, perhaps even millions. But the importance of the operations that must be performed, the complexity of the technique—in a word, its difficulty and the long and minute post-operative care required—does not permit one to undertake it without long preparation. To avoid failure, and the disrepute which has befallen the first attempts in the surgical therapy of deafness, we must envisage three facts:

1. *For the otologists:* There should be an organization of teams, truly and thoroughly specialized, instructed minutely and during a given length of time, sufficiently numerous to answer a great number of calls and avoid fatigue and hurry.

2. *For the patients:* It must be possible to hospitalize them the necessary time, in quarters specially chosen for them, far from the neighborhood of other suppurating diseases, acute or chronic, of the ear or the nose, and in a condition of mental and material hygiene that is necessary and suitable for patients who undergo labyrinth operations.

3. Lastly, *in order to realize further progress:* There must be an organization of laboratories, with adequate quarters and precise acoumetric apparatus.

Such a realization would make of otology a highly evolved specialty, perhaps even similar to ophthalmology, which has attained, in such a short space of time, a high degree of perfection. But, as I have said already, in Europe this cannot be the result of isolated efforts. In order to obtain the indispensable help of public and government authorities, one must first of all have the approbation and the moral help of an international committee of otosclerosis, which is the supreme judge in this matter, and the only one qualified to provoke the necessary decisions. I should be especially happy, if, in spite of the gaps and the imperfections of such a long and arid discourse, I have been able this evening to retain your kind attention on the real possibility, the unavoidable necessity, and the profoundly humane character of this great work that remains to be accomplished.

THE EVALUATION OF THE SURGICAL TREATMENT OF HYPERTENSION*

GEORGE J. HEUER

It is always difficult and frequently unwise to attempt to evaluate methods of treatment on the basis of insufficient data. The surgical treatment of hypertension must still be considered an experiment in the therapeutics of the disease. The varying manifestations and clinical course of hypertension make it necessary that the results of surgical treatment be studied over a period of years before they properly can be evaluated. It is quite beyond me to predict at the present time the ultimate value of surgical methods. What I can do is to relate our own experience in the treatment of the disease, collect and present the experience of other surgeons as reported in the literature, attempt to correlate the clinical and experimental work which has been done and, from all this, make some guarded statements regarding the surgical treatment of hypertension.

Based upon the supposed relationship between hypertension and certain glands of internal secretion, the sympathetic nervous system and the peripheral vascular system, various surgical procedures have been proposed and used in the treatment of the disease. I shall attempt to present to you all the available data regarding them. I shall omit the treatment of hypertension by radiation of the hypophysis as being outside my present text.

I. *The Adrenal Gland; its relationship with hypertension and the therapeutic measures based upon this relationship.* A number of observers have concentrated their attention upon the adrenal gland as a means of attack on hypertension. They conceive of hypertension as the result of hyperfunction of the adrenal glands, the excessive amount of adrenalin excreted into the circulation causing vasoconstriction. I shall not here set forth the evidence

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on which this theory of hyperadrenalinemia is based. It has been summarized admirably by Fishberg, to whom reference may be made by those interested. Clinically the evidence is far from conclusive. Experimentally a relationship between hypertension and excessive adrenal secretion does not yet appear to have been established. Nevertheless, surgeons have attacked the adrenal glands in patients with hypertension and by one of two methods—total denervation of the adrenal glands or subtotal adrenalectomy.

(a) *Total denervation of the adrenal glands.* No one has had an experience with the operation of adrenal denervation comparable to that of Crile. Moreover, in a fairly comprehensive survey of the literature I find but few reports, other than those of Crile, of adrenal denervation for essential hypertension. From the various publications of Crile, the conclusion seems to be justified that total denervation of the adrenal glands for essential hypertension has failed to give satisfactory results. He notes that in cases in which hypertension is accompanied by "nervousness, heart-consciousness and tachycardia" these manifestations are often relieved. He also notes that in early essential hypertension in young subjects there is evidence that denervation may stabilize the process, so as perhaps to lessen the percentage of vascular accidents. However, the results of this procedure in the treatment of essential hypertension have been disappointing.

(b) *Subtotal adrenalectomy.* The rationale of this procedure is similar to that in the treatment of exophthalmic goiter. It is assumed that if the subtotal removal of the thyroid gland improves or cures the symptoms of hyperthyroidism through the reduction of thyroid secretion, the subtotal removal of the adrenal gland should, by the reduction of one of its secretions, adrenalin, improve or cure the important symptoms of essential hypertension. A search of the literature has shown twenty-eight cases of evident or presumed essential hypertension treated by subtotal adrenalectomy. The operation has consisted in the partial removal of one gland,

the total removal of one gland or the subtotal removal of both glands. Of the twenty-eight cases, twenty-six have been collected and studied by Meillere and Olivier. The results of their studies show that of the twenty-six cases, four died very soon after operation, four failed to show the slightest benefit, nine were improved in the sense that their subjective symptoms were lessened and their blood pressure reduced, and nine were so greatly improved that the operation was considered a success. The two additional cases which I have found in the literature are considered successful. When I analyze the cases as reported by Meillere and Olivier and add the two cases not included in their report, I find that eleven surgeons operating upon twenty cases had three more or less successful results, and that one surgeon operating upon eight cases had eight successful results. Because of these discrepancies in the results obtained I have consulted the original sources in all reported cases. I cannot here detail this study but I may summarize it as follows:

1. Three cases, perhaps, should be excluded from consideration as not pertaining to the problem of essential hypertension. These are the two cases of DeCourcy, the adrenals of which harbored adrenal tumors, and the case of Rowntree and Ball, in which the adrenal was explored but was left untouched.

2. Four cases died immediately or soon after operation. These include three unpublished cases of Delbet and one case of Meillere and Olivier.

3. Four cases were entirely uninfluenced by subtotal adrenalectomy. These include two cases of Crile and one case each of Stephen and Floercken and Pieri.

4. Eleven cases may be considered under the designation "improved." It is evident that the criteria of a successful operation vary in the minds of different observers, some emphasizing the importance of the improvement of the subjective symptoms, others the importance of the reduction in blood pressure. Viewed from these two standpoints, a study of these eleven cases (Crile two,

Meillere and Olivier two, Stephen and Floercken one, Monier-Vinard and Desmarest two, Pieri, Galata, Wilmoth, and Leriche one each) shows that in all there was some relief or improvement in the subjective symptoms, this being very slight to very considerable. In some cases it continued over the period of observation of the patient (usually a matter of months); in some it was temporary and followed by a recurrence of the original symptoms.

Purely from the standpoint of the relief of or the improvement in subjective symptoms, the eleven cases may be said to have been improved; but this relief in hypertensive patients is subject to the most varied environmental changes. An examination of the blood pressure in the eleven cases before and after operation shows that in two cases (Crile, Stephen and Floercken) the blood pressures were not given; in five cases there was no change in the blood pressure or a very slight change (Meillere and Olivier two, Monier-Vinard and Desmarest two, Pieri); in four cases there was a reduction in the blood pressure. Of these, a case of Crile showed a reduction from 200/110 to 160/92 which would only be significant if the measurements were repeatedly performed; the case of Galata, six months after operation showed a fall from 250/130+ to 220/125 which is not significant; the case of Wilmoth, whose preoperative blood pressure was 300/150, showed a blood pressure two years after operation of 230/145, which is hardly significant as no change in the diastolic pressure occurred; and the case of Leriche showed a fall in pressure from 220 systolic to 180 systolic pressure. Since the latter are single measurements and no diastolic pressures are given, the case is of no value. The effect of subtotal adrenalectomy on the blood pressure in the above cases certainly has not been striking.

5. The six cases of DeCourcy (two above have been excluded) are impossible to appraise due to lack of data. In the two cases of essential hypertension without the association of adrenal tumor, in which protocols are given, the subjective symptoms of one were markedly improved and the blood pressure in both was apparently greatly

reduced, though but single preoperative and few postoperative measurements are given. The fact that in one the last blood pressure observation recorded was made only three days after operation and in the other thirteen days after operation, leaves the results indefinite. Later (December, 1935) DeCourcy reports eighteen cases, but again the results obtained are indefinite.

More recently Friedman and Eisenberg have reported a series of seven cases of hypertension treated either by unilateral or bilateral subtotal adrenalectomy. There were two immediate postoperative deaths. The results in the five cases which survived operation were unsatisfactory both from the viewpoint of a reduction in the blood pressure or from the viewpoint of lasting symptomatic relief.

To summarize the relationship between the adrenal gland and essential hypertension it may be said that a study of patients with essential hypertension has failed thus far to show any conclusive evidence that the cause of the disease lies in the adrenal glands; and that experimental work on animals thus far has failed to show a causal relationship. The surgical treatment of hypertension having as its object an attack upon the adrenal glands has thus far proven unsatisfactory. The statement, you will observe, is based upon a study of the results of Crile of denervation of the adrenal glands and of the results of thirty-five cases of hypertension subjected to subtotal adrenalectomy; an experience possibly too small from which to draw final conclusions.

II. *Chronic Spasm of the Splanchnic Arterioles; its relationship with hypertension and the therapeutic measures based upon this relationship.* There is evidence of the importance of the vessels of the splanchnic area in maintaining the level of blood pressure. This evidence has been summarized by Page and me in various publications. Briefly, it suggests that the splanchnic vessels constitute an important, but not the only, flexible reservoir which governs the level of arterial pressures; and that in essential hypertension the elevated blood pressure is due in part to constriction or loss of elasticity of the splanchnic

vessels. Interruption of what is believed to be the chief vasoconstrictor nerve supply may, then, and does cause a reduction of arterial blood pressure.

Based upon this proposition, another form of surgical treatment of hypertension includes various operations, the purpose of which is to interrupt the sympathetic control of the splanchnic vessels. These operations include the resection of the splanchnic nerves above or below the diaphragm combined with removal of the lower dorsal or upper lumbar sympathetic ganglia; of the removal of the celiac ganglia; and of the division of the anterior nerve roots of a defined region of the spinal cord. I shall discuss these operations in the order named.

(a) *Supradiaphragmatic resection of the splanchnic nerves combined with lower dorsal ganglionectomy.* Danielopolu, impressed with the importance of the splanchnic nerves in the regulation of arterial pressure, suggested in 1923 the division of the splanchnics for the treatment of hypertension. Bruening and Pendé proposed similar procedures. Pieri approached the splanchnic by a supradiaphragmatic route after resection of the 10th, 11th and 12th ribs. Rossi approached the splanchnics between the attachments of the diaphragm after resection of the transverse processes of the 11th and 12th thoracic vertebrae and, if necessary, of the 12th rib. Pereira, objecting to the technics of Pieri and Rossi because of the danger of injury to the pleura, proposed the section of the splanchnics through a subdiaphragmatic route without resection of any bony structures. Craig, having tried both Pieri's and Rossi's technics and having had develop in one case a serious postoperative pneumothorax, turned to Pereira's proposal and devised an approach below the diaphragm which he employed in his later cases.

In the earlier literature and before the extensive use of the procedure by Peet, I find twelve cases of hypertension treated by this method and have consulted the original articles. In ten cases splanchnicotomy was performed only on one side; in two cases it was bilateral. Avoiding

details, I may summarize the results as follows: Pieri's first case and Durante's two cases are not cases of essential hypertension and may be excluded from consideration. The remaining nine cases suffered from hypertension, although it is not clear that all were cases of essential hypertension. The results obtained certainly were not striking. There was improvement in some cases in the subjective manifestations of the disease but no significant changes in the blood pressure occurred. Peet in this country has been the strong advocate of the supradiaphragmatic resection of the splanchnics. While in earlier literature reports concerned, in the majority of cases, unilateral resection, Peet has insisted upon bilateral resection of the major and lesser splanchnic nerves combined with removal of the lower dorsal sympathetic ganglia. The number of patients upon whom he has performed this operation is large (probably over 100) and when the follow-up studies have extended over a sufficiently long period, we should know fairly well what may be expected from this more extensive operation. Thus far the available information regarding Peet's results is as follows: At a meeting of the Clinical Society of Surgery in 1935, Peet stated he had operated upon some sixty cases and gave the results in thirty-nine. Of the thirty-nine cases six, or 15 per cent, showed good results, 43 per cent moderate improvement, 26 per cent slight improvement and 10 per cent no improvement. Two patients died following operation. In January, 1937, in a paper on the effects upon the kidney of bilateral splanchnicotomy in patients with hypertension, he gives the blood pressures of forty-eight patients before and after operation. These patients, the author points out, are not reported to illustrate the effects of splanchnicotomy upon blood pressure in hypertension, and it would therefore be unfair for me to appraise a method from a study of the particular group of cases reported. But his table of cases is of great interest in that it shows the trend with respect to their blood pressure of patients subjected to the operation. In thirty-eight of the forty-eight patients, the blood pressure rather

quickly tends to return to its preoperative hypertensive level; in six this tendency is not striking during the period of observation and in four there is no such tendency to date. In twenty-one patients the blood pressure returned to or exceeded the preoperative hypertensive level, in twelve it approached but did not rise to the preoperative level and in fifteen it remained well below the preoperative level. In these fifteen, ten have been followed six months or less, one has been followed nine months and four have been followed eleven, sixteen, seventeen and twenty-nine months respectively. The results in these four last cases are good.

Other observers have employed the operation as carried out by Peet. In a series of nine cases of essential hypertension, carefully studied by Page, of which seven were examples of mild benign hypertension in which favorable results were to be anticipated, I performed splanchnic resection combined with lower dorsal ganglionectomy. The results have been disappointing. In all, the blood pressure, reduced as a result of the operation, has, over periods of six months to one year, again risen to or exceeded the preoperative level. The results from the viewpoint of the relief of subjective symptoms also have been minimal. Through correspondence and conversations with surgeons about the country I know that others like myself have employed the operation in small series of cases with disappointing results; others believe they have had encouraging results. It will be seen from this discussion that the ultimate value of this procedure, however, cannot yet definitely be stated; all that can be said from the information we have is that it may prove to have a definite value in a small group of cases.

(b) *Subdiaphragmatic resection of the splanchnic nerves combined with removal of the first and third lumbar sympathetic ganglia and partial removal of the adrenal glands.* The operation as described and performed by Adson consists in the exposure through a lumbar approach of the splanchnic nerves after they have perforated the diaphragm. The nerves between the diaphragm and celiac

ganglia are resected, the resection including a part of the celiac ganglion on either side. The first and second lumbar sympathetic ganglia are removed, as is the outer half of each adrenal gland. The operation is performed on both sides with an intervening interval of ten days. Adson's idea is to interrupt all the sympathetic fibers carrying vasoconstrictor impulses to vessels below the diaphragm just as is accomplished by anterior nerve root section. He is not sure that subtotal resection of the adrenal gland is an essential part of the procedure. The operation was first performed by Adson in February, 1935. In 1936, he reported seven cases treated by this method with five good results and two fair results. Later in the same year (October, 1936), he reported twenty-five cases, without a postoperative fatality. Three cases were not improved but of the remainder which presumably were improved he fails to give details. Still later, in February, 1937, he reports forty-five cases treated by this method, of which thirty-eight had been operated upon a period longer than three months, seven a period less than three months. He reports that of the thirty-eight cases followed more than three months after operation, fourteen have an excellent clinical result, ten a good result, three a fair to poor result, while four have failed to show any improvement. Examined from the viewpoint of a reduction in blood pressure nine show an excellent result, eight a good result, eight a fair to poor result, while six have failed to show any reduction. It will be observed that since this operation was first performed in February, 1935, none of the cases at the time of the latest report had lived more than two years, and the majority had lived less than two years after operation. Adson appreciates this but believes he is justified in expressing the opinion that extensive subdiaphragmatic sympathectomy has been of value in relieving patients of clinical symptoms, and in permanently lowering blood pressure. It seems clear from our own experience that sufficient time has not yet elapsed to state the value of the procedure.

(c) *Celiac ganglionectomy.* This more recent operation of Crile consists in the bilateral resection of the celiac ganglion. It involves the division of the major and lesser splanchnic nerves and the interruption of the preaortic sympathetic fibers between the two celiac ganglia. Crile speaks of achieving the denervation of the aorta from the bifurcation to the crus of the diaphragm and states that this is the essential matter in hypertension. Crile, in July, 1936, reported twenty-five cases of malignant hypertension treated by this method but no doubt his series is now much larger. He found that during the operation the blood pressure in cases of malignant hypertension is reduced to the normal level and during the period of hospitalization is more completely stabilized at a lower level than after his former operations. The ultimate results of the procedure cannot at present be stated.

(d) *Rhizotomy or division of the anterior nerve roots of the spinal cord.* The operation consists in the division of the anterior nerve roots of the spinal cord from the sixth dorsal to the second lumbar. The purpose is to interrupt all the sympathetic fibers carrying vasoconstrictor impulses to abdominal vessels below the diaphragm. Unlike the peripheral operations of splanchnicotomy, etc., the preganglionic fibers are interrupted rather than the postganglionic rami; but whether this is of any significance is not at present known. The virtue of the procedure to me has been its probable greater certainty of achieving the desired result. As performed by me the operation has been done in two stages, the first stage consisting in a laminectomy with exposure of the dura mater over the area desired; the second stage consisting in the opening of the dura and the division of the nerve roots. The operation is undoubtedly the most formidable, the most time-consuming and, in one respect, the most dangerous of the operations for hypertension. Its danger lies in the possibility of an accident to the cord with the appearance of symptoms of a transverse lesion. Adson, in 1936, reported twenty-seven cases treated by this method, with good results in thirteen, fair results in six and no improvement

in six. There were two postoperative deaths. Page and I have treated twenty-one patients by this method. The most elaborate preoperative and follow-up studies have been made in them by Page and the results obtained during the period of study can be stated with great accuracy. Of the twenty-one patients one died at the completion of the operation and one died several days after operation. One recovered from the first stage but refused to permit the second stage. One patient, after the first stage, showed signs of a transverse lesion of the cord but when, eight days later, I opened the dura widely, I failed to find a recognizable lesion of the cord. There remain, then, seventeen patients in whom the operation was completed and whom we have followed closely for from one to three years. The results at the present moment in these seventeen patients may be stated as follows:

1. Six patients represent an early stage of essential hypertension. All patients in this group are young women varying in age from 17 to 32 years of age. Symptoms such as headache and shortness of breath were present and usually severe. They exhibited blushing, sweating, lacrimation and palpitation of the heart. Constriction of the retinal arterioles was demonstrable but renal and cardiac changes were minimal. The *average* preoperative blood pressures established after long periods of observation varied between 180 and 210 systolic and 116 and 148 diastolic, the majority having the higher levels. The patients have been followed for from two and a quarter to three years.

In one with a preoperative average blood pressure of 190/122, the blood pressure has remained at 150/96 for three years and the patient is doing a normal person's work.

In one with a preoperative average blood pressure of 206/148, the blood pressure has remained at 138/90 for twenty-eight months and the patient is in excellent shape.

In one with a preoperative average blood pressure of 180/122, the blood pressure has remained at 152/106 for twenty-eight months and the patient is in excellent shape.

In one with a preoperative average blood pressure of 210/130, the blood pressure remained at 140/94 for five months. Since then it has risen and now at thirty months is 170/110. The patient has no subjective complaints and works from 9 A. M. to 6 P. M. every day in a store.

In one with a preoperative average blood pressure of 210/130, the blood pressure remained at 154/104 for fifteen months. Since then it has risen and now at twenty-eight months is 190/118. She has no subjective symptoms and is in good shape.

In one with a preoperative average blood pressure of 210/130, the blood pressure remained at 164/110 for nine months. Since then it has risen and now at twenty-six months it is 220/128. She has no subjective complaints and works at her profession of nursing.

Of these six patients who represent a stage of the disease which would appear to be most favorable from the standpoint of treatment, three have had a satisfactory reduction of blood pressure which has persisted for from twenty-eight to thirty-seven months. The remaining three had a satisfactory reduction in blood pressure for five, nine and fifteen months respectively after operation; then a gradual rise which at the end of from twenty-six to thirty months, approaches but does not equal the preoperative level in two cases, and exceeds the preoperative level in one case. The improvement in the subjective symptoms in all patients has been striking and thus far has been permanent.

2. Three patients represent a severe benign hypertension with *moderate* vascular changes. There was some variation as to the rate at which the morbid process was advancing. In one patient severe secondary glaucoma developed and in another, attacks resembling transient apoplexy. The subjective symptoms were not especially marked. The *average* preoperative systolic blood pressures varied between 240 and 260, the *average* diastolic pressure varied between 140 and 160.

In one with a preoperative average blood pressure of 258/140, the blood pressure has remained at 208/126 for

twenty-three months. The case is one of fixed hypertension of ten years standing. There is subjective improvement.

In one with a preoperative average blood pressure of 240/150, the blood pressure has remained at 210/132 for ten months. There is subjective improvement and the attacks of unconsciousness (transient apoplexy) have not reappeared since operation.

In one with a preoperative average blood pressure of 260/160, the blood pressure fell to 192/130 for three months; since then it has risen and now at ten months is 256/156. The glaucoma and headaches disappeared immediately after operation and have not reappeared.

It is evident in these three patients with severe benign hypertension, but with only moderate demonstrable vascular changes, that the effects of the operation on the blood pressure have been slight. The subjective improvement in two of the three cases has been marked.

3. Three patients represent a severe benign hypertension with *marked* vascular changes. The disease was of long duration. Evidence of marked vascular changes was found in the eyegrounds, peripheral vessels and muscle removed at operation. There were demonstrable cardiac and renal changes. The blood pressure, especially the diastolic pressure, was regularly high.

In one with a preoperative average blood pressure of 190/122, the blood pressure has remained at 176/112 for twenty-six months. She is in good shape and doing well.

In one with a preoperative average blood pressure of 270/160, the blood pressure remained at 240/150 for sixteen months when renal insufficiency rapidly appeared. He died seventeen months after operation. For sixteen months after operation he led an active life.

In one with a preoperative average blood pressure of 230/142, the blood pressure remained at 210/122 for nine months when she died of apoplexy. The relief of headaches was striking.

In these three patients the blood pressure was not reduced significantly. One patient with a blood pressure

stabilized at 176/112 for twenty-six months is doing well. Two patients died from the disease, nine and seventeen months after operation. During these periods they had striking relief from their subjective symptoms.

4. Five patients represent the highly malignant type of hypertension. The disease was of short duration but within this period the vascular change was extreme. Marked neuroretinopathy was present in all these patients. In two, cardiac and renal changes were advanced, in two, they were moderate and in one, they had just appeared.

In one with a preoperative average blood pressure of 190/120, the blood pressure has remained at 150/100 for twenty-three months. His subjective symptoms disappeared and have not recurred. His papilledema and retinal exudates disappeared and have not reappeared. He lives an active outdoor life and is in excellent shape.

In one with a preoperative average blood pressure of 208/132, the blood pressure remained at 186/120 for seven months; since then the systolic pressure has risen and now at fifteen months is nearly at the original level, while the diastolic pressure has continued at its lower level. His subjective symptoms have disappeared. There has been definite improvement in the ocular fundi and no new hemorrhages or exudates have appeared. The disease, thus far, has been remarkably retarded.

In one with a preoperative average blood pressure of 190/124, the blood pressure remained at 184/122 for ten months. The papilledema disappeared. The patient's subjective symptoms disappeared and he felt in excellent health. Ten months after operation the patient was readmitted with cardiac and renal failure and died.

In one with a preoperative average blood pressure of 270/170, the blood pressure remained at 210/140 for two months. The papilledema markedly diminished, the subjective symptoms improved. Two months after operation he died with left hemiplegia.

In one with a preoperative average blood pressure of 200/110, death occurred on the operating table just after

the completion of a one-stage operation in which seven anterior roots on each side were divided. The patient was an example of hopeless malignant arteriolar nephrosclerosis with neuroretinopathy, detachment of the retina, cardiac hypertrophy and hypertension. It was one of our early cases and in view of our later experience should not have been subjected to operation.

Of these five patients, then, with a highly malignant type of hypertension, one at the end of twenty-three months has an excellent result, and one at the end of fifteen months has a good result but has again an elevated blood pressure. Two patients died from the disease; one ten months, the other two months after operation. In the intervals after operation their blood pressures were reduced and their subjective symptoms were greatly improved, as were the objective changes in their eyegrounds. One patient died immediately after operation.

Summarizing the whole series I may say: In early mild hypertension in young women, four of six patients have had a satisfactory reduction in blood pressure and relief of subjective symptoms for from two and a third to three years. Two of six patients have had complete relief of subjective symptoms, are in good health and doing their usual work twenty-six and twenty-eight months after operation; but their blood pressures, after being reduced satisfactorily for nine and fifteen months, have again risen to approximately preoperative levels.

In severe benign hypertension, three patients show a slight but an unsatisfactory reduction in blood pressure. They show, however, marked subjective and objective improvement at the end of ten to twenty-three months.

In severe benign hypertension with marked vascular changes, one of three patients has had a fairly satisfactory reduction in blood pressure for twenty-six months and is in good physical shape with a minimum of subjective symptoms. Two of three patients showed a definite reduction of blood pressure but died of the disease sixteen and nine months respectively after operation. The relief of

subjective symptoms was striking and one led an active life for over a year after operation.

In severe malignant hypertension, one of five patients has had a satisfactory reduction in blood pressure and he leads an active normal life two years after operation. One had a considerable reduction in blood pressure for seven months, but at the end of fifteen months his systolic pressure nearly equals his preoperative pressure, while his diastolic pressure remains satisfactorily reduced. He is greatly improved. Three of the five patients died—one immediately after operation, one two months after operation and one ten months after operation.

Discussion: It must be evident from this summary of the various surgical methods which have thus far been used in the treatment of essential hypertension, how far we are from knowing accurately their ultimate value. A study such as this shows clearly the necessity of accurate and repeated observations over a fairly prolonged period before treatment is undertaken; and of a period of follow-up studies which must be continued over years rather than over weeks or months. It would be rash to attempt to appraise the value of these methods from the meager information we have; but I may, perhaps, from the clinical and experimental data available, discuss what may be expected of them.

The cause of hypertension is not as yet known. The occurrence of the disease under such a variety of conditions suggests perhaps that no single cause is responsible for its initiation. Ablation experiments on normal and hypertensive animals and clinical observations on human subjects fail to indicate definitely that any of the glands of internal secretion (such as the hypophysis, adrenal, ovary, thyroid or pancreas) are primarily at fault. While the proof of the matter must await further clinical experience, it does not appear likely that therapeutic attacks directed at single glands of internal secretion such as the irradiation of the hypophysis or subtotal adrenalectomy will solve the problem of the treatment of the condition. Nor is there any convincing evidence as yet that the morbid

process in essential hypertension lies exclusively in the central nervous system. While it appears that the splanchnic vessels contribute an important flexible reservoir which governs the level of arterial pressure, both clinical and experimental data indicate that a peripheral motor mechanism residing in the blood vessels themselves may sustain the blood pressure even at an elevated level. This is indicated by the eventual rise in pressure following complete destruction of the spinal cord below the seventh cervical segment in animals and by an accumulating clinical experience following resection or division of sympathetic nerves controlling the vessels of the splanchnic area. Viewed in the light of this experience, the surgical operations of supra- or sub-diaphragmatic splanchnicotomy, celiac ganglionectomy and anterior spinal nerve root section are likely in the long run to be only partly effective; for, if we grant that they do not attack directly the cause of the disease, they can affect only that part of the blood pressure controlled by the sympathetic fibers which they interrupt. Our studies on the effects of anterior nerve root section, however, show that in the early mild hypertension and even in malignant hypertension the tendency of the blood pressure after operation to rise and again approach the preoperative level may not be apparent after two to three years; and it is possible, though not yet proven, that the interruption of the sympathetic fibers controlling the splanchnic area may cause, in certain cases, the identification of which is not yet possible, a permanent reduction in blood pressure.

While, then, the permanent effects of our surgical procedures with respect to the blood pressure in hypertension have not been established, their effects upon the subjective and some of the objective manifestations of the disease appear more certain. With scarcely an exception in our experience, anterior root section has caused a striking improvement in headaches and other subjective symptoms of the disease; an improvement so satisfactory to the patients as to justify the operation on this basis alone. Equally striking is the disappearance of papilledema,

hemorrhage and exudates in the eyegrounds; changes for the better which may follow what seems an insignificant reduction in the blood pressure. Such results are not readily explained but they continue to excite our interest. I have observed, as have others, patients with essential hypertension incapacitated and practically bed-ridden as a result of the disease, returned to their customary work for a period as long as three years; an experience which encourages me to continue to explore the possibilities of surgery in its treatment. What surgical procedure will prove to be the most productive of lasting benefit consistent with reasonable safety to the patient remains at the moment undecided.

PRERENAL AZOTEMIA AND THE PATHOLOGY OF RENAL BLOOD FLOW*

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Deficient urinary elimination with resultant azotemia and uremia results not only from intrinsic disease of the kidneys and urinary passages, but may also be a reflection of pathological processes in other parts of the body. From the point of view of the sequence of events in the elaboration of the urine, one may speak of nitrogen retention of the latter category as *prerenal azotemia*—in contradistinction to renal azotemia due to primary disease of the kidneys and postrenal azotemia resulting from obstruction of the urinary passages. This discussion will be confined to the renal and prerenal azotemias, leaving the nitrogen retention that so often results from lesions of the urinary passages to the urological section of the program.

THE FUNDAMENTAL CRITERION OF IMPAIRMENT OF RENAL FUNCTION

To the clinician, *the outstanding and defining characteristic of impairment of renal function is a concentration of the urine disproportionately low in comparison to the urinary volume.* Thus, if a hypertensive patient with obvious heart failure passes a random specimen of urine which is deeply colored and obviously of high concentration, the inference is warranted that renal function is not significantly impaired. On the other hand, if the urinary volume is small, say 400 c.c. in 24 hours, and nevertheless the urine is pale and of low concentration, one may conclude that renal function is severely impaired. Analysis of tests of renal function which have proved of value shows that they include as a fundamental factor the concentration of one or more urinary constituents. In the light of the mechanism of the elaboration of the urine, it is not surprising that the concentrating ability of the kidney is a trustworthy index of its functional

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capacity. While many of the details of kidney function are still obscure, their integration is almost entirely expressed in the transference of substances preformed* in the plasma to the lumen of the urinary tubules, chemically unchanged but mostly in far higher concentration than in the plasma. Concentration of the potential urinary constituents in the plasma is the fundamental accomplishment of the kidney, and measurement of the concentrating ability of the kidney mirrors the functional capacity of the organ.

The Stages of Impairment of Renal Function

In evaluating the significance of impairment of renal function for the organism as a whole, it is to be borne in mind that the kidney, like most other organs, is endowed with a large factor of safety; the healthy kidney is able to master a far greater excretory load than ever presents itself in the usual course of life. On the basis of the ensuing systemic manifestations, one may differentiate three stages of impairment of renal function:

1. A latent stage in which the impairment of renal function is so slight as only to narrow the factor of safety and have no deleterious effect on the organism. This stage can be demonstrated only by means of tests of renal function which show, for example, that the urea clearance is diminished or the maximum specific gravity in the concentration test is subnormal. But the blood chemistry is unaltered and the 24-hour urinary volume is not increased. Of course, if in this latent stage of impairment of renal function the kidney is confronted by a very heavy burden, it will fall behind the accomplishment of a healthy kidney. An illustration is not uncommonly furnished when urea is given in large doses as a diuretic in the nephrotic syndrome; the urea content of the blood then rises to higher levels than is usually the case with corresponding doses in the presence of healthy kidneys.

* The urinary constituents, notably ammonia and at least some of the hippuric acid, which are synthesized by the kidney itself appear to be few in number.

2. In the second stage of impairment of renal function, the concentrating ability of the kidney is diminished, but this is atoned for by increase in urinary volume so that the urea content of the blood remains at a normal level. In analogy with the terminology customary in heart disease, the teleologically-minded may speak of compensated impairment of renal function. This stage is characterized by pronounced diminution in the maximum specific gravity of the urine in the concentration test accompanied by normal urea content of the blood. The urea clearance may be either subnormal or normal; as a result of increase in urinary volume, a normal urea clearance may be obtained despite diminution in the urea concentration in the urine. While symptoms due to retention of urinary constituents are of course absent in this stage of compensation, the polyuria may be manifested by frequency of urination during the day and nocturia, as well as objectively by a dry skin. In forms of the contracted kidney which are but slowly or not at all progressive, this stage of compensated impairment of renal function with polyuria but no retention may last for years.

3. In the third stage of impairment of renal function, the accomplishment of the kidneys fails to master the excretory load with consequent retention of urinary constituents in the blood and tissues. The resulting clinical picture is known as uremia.

Pathogenesis of Uremic Symptoms

The term uremia was introduced a century ago to mean urine in the blood, and since then the conception has been dominant that the symptoms are due to poisoning by retained urinary constituents, i.e., that uremia is purely an auto-intoxication by katabolic products which fail of elimination by the kidney. In addition to urea, creatinin, and other resultants of endogenous metabolism, products of intestinal putrefaction, including highly toxic phenol derivatives, accumulate within the body. Of late years, however, it has become clear that by no means all the symptoms of uremia are of such toxic origin. Another

factor that is undoubtedly of great importance in many instances is excessive loss of water and certain electrolytes in the urine with resultant dehydration and demineralization of the organism. We have seen that already in the compensated stage of impairment of renal function, the polyuria evoked by the impairment of concentrating ability may produce dehydration of the organism. With advance to the decompensated stage, the dehydration may become much more severe; in fact, patients with long-standing severe impairment of renal function present extreme dehydration, in the pathogenesis of which the polyuria is abetted and later supplanted by gastro-intestinal disturbances, which on the one hand interfere with the absorption of water and on the other hand result in loss of water by vomiting and diarrhea. Demineralization is also a consequence of severe impairment of renal function. The functionally impaired kidney is not able to form as much ammonia from urea as the intact organ, nor is it able to elaborate as highly acid a urine as in health. To substitute for ammonia in neutralizing the predominantly acid end products of metabolism, the fixed base of the body is drawn upon and thus lost in the urine. Moreover, Peters has found that the insufficient kidney excretes chloride at lower plasma chloride levels than in health. These and other factors, especially vomiting, diarrhea and inadequate absorption when gastro-intestinal disturbances are present, serve to deplete the electrolytes of the body in many uremic patients. In the case of calcium, the plasma content is further lowered in consequence of phosphate retention and the frequently depressed protein content of the plasma. In addition to the symptoms which result from exsiccation of the tissues, it will be seen later that dehydration can further lower the functional efficiency of the kidney and thus, initiating a vicious circle, in turn aggravate the severity of uremia. One manifestation of the derangement in mineral metabolism due to renal insufficiency to which attention may be briefly called at this juncture is renal rickets. It has long been known that renal insufficiency of sufficiently long duration in childhood, when skeletal

growth is most active, may result in severe skeletal deformities, the so-called renal rickets. It seems very plausible that the demineralization of the skeleton due to long-standing renal insufficiency is of primary importance in the pathogenesis of this remarkable skeletal dysplasia.

There are thus two general ways in which renal insufficiency acts deleteriously on the organism: 1. By causing retention of various substances which should be excreted in the urine; 2. By producing dehydration and demineralization of the body in consequence of excessive excretion of water and certain electrolytes. The acidosis which is often prominent in the symptomatology of uremia results from both these factors. Impairment of the synthetic functions of the kidneys also have harmful effects but this is probably largely, as we have already seen in the case of ammonia, through the two mechanisms just mentioned. That the organism suffers in renal insufficiency as a result of loss of an internal secretion of the kidney is as yet purely hypothetical.

The recent realization of the significance of the disturbance in water and salt metabolism in uremia parallels a similar development in the other classical auto-intoxication, diabetic coma. Both diabetic coma and uremia were long considered almost pure poisonings, in the one instance by ketonic acids, in the other by urinary constituents. This is probably largely true when they arise suddenly, as in the uremia of acute urinary suppression or obstruction, or in diabetic coma in a young diabetic previously well controlled and without glycosuria who develops an acute infection or discontinues insulin. But the situation is different when the uremia climaxes a long period of renal insufficiency or the diabetic coma terminates protracted severe glycosuria and ketonuria. Here the previously existing dehydration and demineralization become accentuated and participate importantly in the pathogenesis of the final picture. It is this common feature of dehydration and demineralization that largely accounts for the striking analogies in the clinical pictures of many instances of uremia and diabetic coma.

Prerenal Azotemia

In the foregoing we have considered renal insufficiency and consequent azotemia due to disease of the kidneys, in which the structural alterations in the glomeruli and tubules seem adequate to account for the renal failure. We now turn to another type of defective renal excretion and resultant azotemia in which, while there may be severe depression of renal function, this is not accounted for by the morphological changes in the kidneys, for the latter may be absent or no more considerable than are often to be found at the postmortem examination of individuals without renal insufficiency. As already mentioned, this form of nitrogen retention may logically be termed *prerenal azotemia*. This term is preferable to the designation extrarenal azotemia, which has frequently been used, for the latter fails to differentiate from the common azotemias due to obstruction of the urinary passages. Knowledge of the prerenal azotemias dates back to the observation by Tileston and Comfort in 1913 that pronounced enhancement of the nonprotein nitrogen of the blood results from intestinal obstruction with vomiting. Only in the past few years, however, has there been general appreciation of the frequency of the prerenal azotemias—a realization that has been reflected in therapeutic results.

Before discussing the pathogenesis of the prerenal azotemias, it may be worth while to enumerate the most important circumstances in which they occur.

Occurrence of the Prerenal Azotemias

1. Severe and protracted vomiting, such as is encountered in pyloric and intestinal obstruction and hyperemesis gravidarum. In chronic intestinal obstruction without vomiting but with accumulation of enormous volumes of intestinal contents in the dilated loops of gut, the nonprotein nitrogen of the blood may rise. In the uremia of organic renal disease, vomiting may add a prerenal to the renal factor in the causation of the azotemia.

2. Immoderate loss of intestinal contents in diarrhea or rarely duodenal fistula. Azotemia of this origin occurs

commonly in infants but is rare in adults, apart from cholera, unless there is complication by vomiting so that the lost fluid and salt is not replaced.

3. In certain affections of the liver and biliary passages. Not very rarely, when convalescence seems smoothly initiated after operations on the gall bladder or common duct, after an interval of from one to six or even more days, malaise develops, the temperature rises, oliguria sets in, the nonprotein nitrogen of the blood rises, the patient becomes restless and then perhaps delirious or comatose, and may succumb with the clinical picture of uremia. A similar picture has been observed following traumatic pulpification of the liver and may occur during acute liver degeneration or in acute exacerbations of chronic liver disease. While marked degeneration of the renal tubules may be found at necropsy, in other cases, despite azotemia and the clinical picture of uremia, little morphological change in the kidneys is demonstrable. The syndrome just described has been spoken of as the "hepato-renal syndrome" or "liver death," and is one of the chief dangers of those undergoing gall bladder surgery.

4. In diabetes with acidosis, either in coma or precoma, or in the complete absence of cerebral symptoms with only such complaints as weakness or loss of weight, marked nitrogen retention may be found. The azotemia may continue to mount after the patient has been brought out of coma by insulin. Significant azotemia is present in about half of comatose diabetics. The azotemia usually occurs only after a protracted period of acidosis with polyuria and rarely in previously well controlled diabetics who have gone into coma rather abruptly as a result of cessation of insulin or an infection.

5. In the crises of Addison's disease there is a rise in the nonprotein nitrogen of the blood. The same occurs in much more pronounced degree in experimental removal of the suprarenal glands and is so characteristic that it has served as a means for testing the potency of cortical extracts.

6. In traumatic shock the nonprotein nitrogen of the blood often rises to considerable heights.

7. In postoperative collapse (surgical shock) there may be pronounced azotemia.

8. In the circulatory collapse of pneumonia, diphtheria, sepsis, peritonitis, and other infections, the nonprotein nitrogen of the blood may attain high levels.

9. In widespread burns with shock, there may be great azotemia.

10. In coronary thrombosis with shock, the nonprotein nitrogen occasionally rises notably and may exceed 100 mg. per cent. Nitrogen retention was present in five of six fatal instances of myocardial infarction studied by Steinberg.

11. Following profuse hemorrhage, notably from the gastro-intestinal tract, azotemia may appear and even surpass 100 mg. per cent of nonprotein nitrogen. Alsted found the blood urea increased in 12 of 25 patients with hematemesis and melena.

Clinical Picture of Prerenal Azotemia

In each of the variegated circumstances just enumerated, the following syndrome may develop:

1. A symptomatology akin to that accompanying renal insufficiency due to primary renal disease. As in patients with Bright's disease, considerable degrees of azotemia may exist without reflection in the clinical symptoms, while in other cases there is progressive muscular and mental asthenia deepening to coma, vomiting, diarrhea, a urinous breath, and the other classical manifestations of uremia, including rarely pericarditis.

2. Increase in the nonprotein nitrogen of the blood due not only to rise in urea but also involving creatinin and uric acid; the other nonprotein nitrogenous constituents have hardly been studied, apart from observations of increase in amino-acids in some instances of hepatic disease.

3. Decrease in the chloride content of the plasma is the rule but, it is to be emphasized, is by no means constant.

Depending on the underlying condition there may be either acidosis (as in diabetic coma and Addison's disease) or alkalosis, as is most often the case in azotemia due to vomiting.

4. Usually there is pronounced oliguria, which may go on to anuria. However, especially in the cases due to diabetic acidosis but also occasionally in liver disease, there may be a stage of pronounced polyuria, even 2000 c.c. of urine daily, despite pronounced and mounting azotemia.

5. The urine is usually of rather high specific gravity at the onset, and this may persist throughout. However, in many of the cases one is able to trace a progressive decrease in specific gravity so that this may be no higher than 1.010 despite azotemia and marked oliguria.

6. The urine may reveal no abnormal constituents. But moderate albuminuria may appear; it may be accompanied by red cells as well as hyalin and granular casts in the sediment.

7. Most often there are definite evidences of peripheral circulatory failure resulting in shock of more or less severity. The more carefully one follows the course of the cases, the more often the signs of peripheral circulatory failure are to be detected. When pronounced, the peripheral circulatory failure is manifested by pallor with or without greyish cyanosis, sweating skin, cold extremities, most often a fall in arterial pressure, and, what is most characteristic, collapsed peripheral veins with low venous pressure.

8. Frequent remarkable improvement with decrease in azotemia as a result of the intravenous administration of salt and sugar solutions.

Pathogenesis

We may now turn to the important, interesting and, it may be remarked at the onset, as yet largely unsolved problem of the pathogenesis of prerenal azotemia. The first question that arises is the following: Is the accumula-

tion of potential urinary constituents in the blood due to augmented break-down of body protein or is it due to decreased accomplishment of the kidney? In other words, is the azotemia due to overloading of the kidneys or to failure of the kidneys?

INCREASED DESTRUCTION OF PROTEIN.—Studies of nitrogen excretion in the urine have shown that there is increased protein destruction in at least many of the conditions leading to prerenal azotemia—the alimentary toxicosis of infants, diabetic acidosis, acute affections of the liver, etc. Such increased protein destruction must tend to augment the nonprotein nitrogen of the blood when the kidneys are insufficient. But that the increased protein destruction in these conditions is sufficient to produce pronounced azotemia in the presence of unimpaired renal excretion is very unlikely. When kidney function is good, one can administer quantities of urea far greater than those resulting from even very greatly accelerated protein katabolism without producing more than slight increase in the urea content of the blood. I have repeatedly given 75 or even 100 grams of urea daily for a week or longer to patients with cardiac edema without increasing the urea nitrogen content of the blood to more than 30 or 40 mg. per cent. On the other hand, when renal function is impaired, as it often is in patients with edema due to glomerulo-nephritis, the administration of urea may cause a considerable increase in the urea content of the blood. The factor of safety of the kidneys appears to be so great that when their function is unimpaired they are able to eliminate the end products of the most extreme acceleration of protein metabolism occurring in disease with little accumulation of these substances in the blood. It thus seems fair to conclude that increase in the nitrogenous end products of metabolism is at most an accessory factor in pronounced prerenal azotemia, and that when considerable azotemia is present, one must conclude that renal excretion is subnormal.

IMPAIRMENT OF KIDNEY FUNCTION.—Tests of kidney function afford direct evidence of the functional impair-

ment of the kidneys in prerenal azotemia. This is contrary to an opinion previously held by the speaker, which was based on the observation of high specific gravity of the urine in prerenal azotemia. However, the concentration of the urine can be rationally interpreted only in the light of the urinary volume. As already emphasized, the fundamental criterion of impairment of renal function is a concentration of the urine disproportionately low in comparison to the volume. Thus, while a specific gravity of 1.020 is evidence of good kidney function when the urinary volume is normal or but little reduced, it is too low if the urinary volume is very small, say under 400 c.c. in 24 hours. Such a disproportionately low concentration of the urine is demonstrable in at least the vast majority of instances of prerenal azotemia. It is true that sometimes the specific gravity and urea concentration of the urine are so high that the concentrating ability seems unimpaired. Thus, the specific gravity may exceed 1.030 and the urea concentration even reach 5 per cent, the latter of which is close to the maximum urea concentration of which even the healthy human kidney is capable. In such instances, the possibility is to be considered that the azotemia is due purely to extreme diminution in urinary volume, perhaps associated with augmented breakdown of protein, in the absence of the decreased concentrating ability which bespeaks impairment of renal function. But in the vast majority of patients with prerenal azotemia, comparison of the specific gravity with the urinary volume shows that the concentrating ability is definitely decreased. Not uncommonly, if one follows the course of the case, progressive impairment of the concentrating ability is evident. At the start the oliguria is accompanied by a fairly high specific gravity of the urine, which then progressively decreases despite the fact that the urinary volume does not rise and may also decrease. I have repeatedly seen exquisite examples of such a course of events in prerenal azotemia due to vomiting, to diabetic acidosis, to liver disease, and to hemorrhage. In such instances, the specific gravity of the urine may become

fixed around 1.010 despite oliguria, just as occurs in primary renal diseases. It may be several days after the cause of the prerenal azotemia has disappeared before the concentrating ability of the kidneys is restored. Thus, in a recent patient with vomiting and diarrhea due to gastroenteritis, in whom the nonprotein nitrogen of the blood exceeded 100 mg. per cent and whose urinary specific gravity was fixed close to 1.010 in two concentration tests, it was almost a week before the concentrating ability returned. The urea clearance test also shows the impairment of renal function in prerenal azotemia; very low results may be obtained. Experimentally, the decrease in concentrating ability in prerenal azotemia has repeatedly been demonstrated. McQuarrie and Whipple long ago showed that in dogs with azotemia due to the vomiting of intestinal obstruction, the urea concentration ratio is decreased. In dogs in which dechloridation was produced by a low chloride diet and repeated vomiting, Ambard found that the maximal concentration of urea in the urine dropped to a third of its previous value.

Mechanism of Impairment of Renal Function in Prerenal Azotemia.—The next question that arises is that of the mechanism of the impairment of renal function leading to prerenal azotemia. The anatomical findings do not answer the question. In all the conditions enumerated—vomiting, diabetic acidosis, Addison's disease, liver disease, traumatic shock, postoperative collapse, hematemesis, etc.—the patient may succumb with severe impairment of the concentrating ability of the kidney and azotemia, and yet the necropsy reveals little change in the kidneys. These are the cases that have been described as uremia with intact kidneys. In some instances neither the glomeruli nor the tubules show appreciable changes. More often, while the glomeruli are intact, the tubules are the seat of moderate regressive changes, such as cloudy swelling, hyalin-droplet degeneration, fatty change, or even necrosis of isolated cells. However, such changes in the tubular epithelium are the rule in patients who succumb to any protracted illness, and may occur with

like or greater intensity in persons with the same underlying condition but no azotemia. Much less often, there is widespread necrosis of the tubular epithelium; this and the focal calcification which sometimes occurs will be discussed later. Nevertheless, the fact that the large majority of the cases present no significant anatomical changes at post mortem shows that the explanation of the azotemia must be sought in factors which depress kidney function although they are not documented by structural alterations revealed by present morphological methods.

Among the factors which have been thought to be concerned in depressing the accomplishment of the kidneys and thus producing azotemia are the following:

1. *Hypochloremia.* In many forms of prerenal azotemia there is decrease in the chloride content of the blood. This is usually especially pronounced in conditions with vomiting. The intravenous administration of sodium chloride solution may result in prompt improvement with decrease in azotemia. On the basis of these facts, it has been thought that decrease in the chloride content of the blood may cause azotemia; the French speak of *azotémie par manque de sel,* and the expression hypochloremic azotemia has gained considerable currency. Some have advocated a teleological explanation of the connection between hypochloremia and azotemia; retention of urea in the blood, through unexplained mechanisms, is thought to compensate for the fall in osmotic pressure due to the diminution in chloride. However, this conception is scarcely tenable; urea passes through biological membranes so readily that it soon attains equal concentration in blood and most tissues so that it would not compensate osmotically for decrease in the concentration of an electrolyte in the blood. Others have thought that hypochloremia entails azotemia through the intermediacy of impairment of renal function. We have already seen that impairment of renal function is actually responsible for the azotemia. But there is no evidence that hypochloremia, even when present, is *specifically* responsible for the impairment of renal function. Almost all forms of prerenal azotemia may occur

in the absence as well as in the presence of hypochloremia. Even the fact that the azotemia is diminished by the administration of sodium chloride does not prove that chloride deficiency *per se* is responsible for the nitrogen retention. Infusions of sodium chloride solution may have this effect in the absence of hypochloremia, for example in traumatic or postoperative shock or in the azotemia which follows hemorrhage. As will be seen later, the impairment of renal function seems to be correlated with dehydration and decrease in circulating blood volume, and when hypochloremia is present it participates in the pathogenesis of the impairment of renal function only to the extent of, and through its role in, the production of dehydration and decrease in circulating blood volume.

2. *Low arterial pressure.* The conditions leading to prerenal azotemia are frequently accompanied by low arterial tension. It has been thought that the low arterial pressure impairs renal function with resultant azotemia. That sufficient fall in arterial pressure must affect renal function adversely would be anticipated from the known importance of glomerular filtration in the elaboration of the urine and from the results of animal experiments, which have shown that profound fall in general arterial pressure is accompanied by diminution in urinary volume. When the arterial pressure falls to shock levels, there seems little doubt that the low pressure is concerned in the pathogenesis of the impairment of renal function and resultant azotemia. But much more often the fall in arterial pressure in patients with prerenal azotemia is not sufficiently pronounced to account for severe impairment of renal function. Often, indeed, there is no fall in blood pressure.

3. *Toxic nephritis.* Damage to the kidney by circulating toxins derived from bacteria or tissue autolysis with resultant "toxic nephritis" has repeatedly been incriminated as the cause of azotemia in such conditions as intestinal obstruction, the intestinal toxicosis of infants, collapse in the acute infections, liver disease, and other

forms of prerenal azotemia. The changes in the tubular epithelium are regarded as manifestations of such toxic damage. However, the actual existence of the toxins in question has not been demonstrated. The often remarkably rapid improvement in renal function following the intravenous administration of salt solution scarcely speaks for toxic damage of the kidney sufficiently severe to produce azotemia. Moreover, the course and clinical accompaniments of the azotemia and anatomical changes in the kidneys in intestinal obstruction and other conditions in which bacterial or autolytic toxins have been suspected is so similar to that in the azotemia of hematemesis, traumatic shock, duodenal fistula, Addison's disease and other conditions in which a circulating toxin seems highly improbable, as to cast doubt on the role of toxins in the former. The conception of a "toxic nephritis" as responsible for the forms of azotemia under discussion thus seems purely hypothetical.

4. *Alkalosis.* Azotemia due to vomiting is most often accompanied by alkalosis. It has been thought that the alkalosis may injure the kidneys and thus produce azotemia. The conception is based largely on clinical observations of renal damage in individuals taking large amounts of sodium bicarbonate for the treatment of peptic ulcer and on the production of renal damage following the long continued administration of alkalis to animals. But that the brief alkalosis in the conditions under discussion damages the kidneys so severely as to produce azotemia has not been demonstrated.

Decreased Renal Blood Flow

None of the factors thus far considered seems to play more than an accessory role in the causation of prerenal azotemia. In the following we shall consider evidence indicating strongly that the primary pathogenetic factor in most, if not all, instances of prerenal azotemia is decrease in blood flow through the kidneys.

In each of the conditions leading to prerenal azotemia—excessive vomiting, hemorrhage, postoperative collapse,

coronary thrombosis, diabetic coma, Addison's disease, etc.—circulatory failure is notoriously apt to develop. The circulatory failure in question is not cardiac insufficiency but primarily peripheral circulatory failure which results in deficient venous return to the heart. It is now known that in at least most forms of peripheral circulatory failure, the deficient venous return to the heart is a manifestation of decrease in circulating blood volume. The clinical picture resulting from pronounced peripheral circulatory failure is that known as shock—pallor or greyish cyanosis, cold extremities, relatively empty peripheral veins, low venous pressure, and usually low arterial pressure. Examination of patients with prerenal azotemia reveals some or all of these evidences of peripheral circulatory failure in more or less pronounced form. Moreover, when therapy directed to the alleviation of the peripheral circulatory failure—which almost always consists in the intravenous injection of glucose or saline solutions or the transfusion of blood intended to elevate the circulating blood volume—is successful, the azotemia clears up *pari passu* with improvement in the other manifestations of peripheral circulatory failure.

Time will not permit the discussion of the mechanisms leading to the peripheral circulatory failure that in turn engenders the azotemia. Suffice it to say that numerous investigators, beginning with those who studied wound shock during the World War, have demonstrated that the large majority of forms of peripheral circulatory failure, if not all, are mediated by a decrease in the circulating blood volume. Such diminution in the volume of circulating blood is brought about by different mechanisms in the individual conditions in which peripheral circulatory failure and consequent prerenal azotemia may develop. In hemorrhage the cause is directly the loss of blood; in traumatic shock apparently seepage of plasma into the traumatized area; in vomiting and diarrhea the loss of fluid and even more of salts produces dehydration; in diabetic acidosis protracted glycosuria and ketonuria entail dehydration; in the crises of Addison's disease there

is a sharp diminution in circulating blood volume apparently correlated with the disturbance in sodium and potassium metabolism; in postoperative collapse a variety of factors combine to produce a negative water balance and consequent dehydration; in burns large volumes of plasma seep from the capillaries onto the denuded surface or into blebs.

In each of these conditions the decrease in circulating blood volume entails a diminished venous return to the heart with an equal fall in cardiac output. This drop in cardiac output is manifested in turn by decreased blood flow through the organs, including the kidneys.

It is, indeed, quite probable, although direct experimental verification is necessary, that the blood flow through the kidneys in peripheral circulatory failure is proportionately more diminished than is the cardiac output. There is ample evidence that with decrease in cardiac output blood flow through all the organs is not equally diminished. The organs which are less immediately vital to the survival of the organism have their blood supply cut down the most. This is accomplished by constriction of the arterioles in these organs. Various investigators have demonstrated directly, by perfusion experiments, that the arterioles in the extremities of an animal in shock are constricted. It is this arteriolar constriction which results in the cold hands and empty veins in the extremities of a patient in shock; the venous pressure in the antecubital veins of such a patient may be less than 1 cm. of water. Presumably, also, constriction of the arterioles is concerned in the generalized pallor or pallid cyanosis of the patient with peripheral circulatory failure. The cutting down of blood flow in relatively nonvital organs was studied quantitatively by Gesell. He showed that when cardiac output is diminished by 10 per cent, the volume of blood flow through the submaxillary gland is decreased 60 per cent, i.e., six times as much. Evidently, when the venous return and consequently the cardiac output is cut down, the blood supply to the immediately vital organs, notably the central nervous system and heart, is maintained at the expense of

lessening the blood flow to the extremities and other not immediately vital parts by vasoconstriction. The teleologically minded may say that the organism is abandoning its outposts in the extremities to defend its capitol in the heart and central nervous system.

Whether the cutting down of blood flow through the kidneys in peripheral circulatory failure is proportionately as great as through the extremities, skin and submaxillary gland, is not known. However, in human shock cardiac output is doubtless diminished far more than the 10 per cent in Gesell's experiment, so that the diminution in blood flow through the kidneys, even though it is proportionally less than the decrease in flow through the submaxillary gland and extremities, may be very great.

That abundant blood flow is a *sine qua non* for adequate renal function has long been known. Various physiological experiments have shown that decrease in renal blood flow is promptly reflected in diminution in urinary volume. Most important from our present point of view, however, are the recent brilliant investigations of Van Slyke and his coworkers in which they measured the volume of renal blood flow in the unanesthetized dog. These experiments established the important result that the urea clearance closely parallels the blood flow through the kidneys, variations in the percentage of urea removed from the blood being less important in the genesis of alterations in the amount of urea excreted. These experiments enable us to understand why peripheral circulatory failure with its diminished renal blood flow is reflected in azotemia.

In view of the role of decreased renal blood flow in the pathogenesis of azotemia in peripheral circulatory failure, it may be asked why the latter so rarely, other than premortally, results from heart failure. Quite probably, one reason is that heart failure is accompanied by increase in capillary pressure, which favors glomerular filtration and thus tends to neutralize the effects of diminished volume of renal blood flow. Moreover, it is improbable that except terminally, when azotemia may occur, heart failure

decreases cardiac output as much as does peripheral circulatory failure.

The conception of the fundamental importance of decreased volume of blood flow through the kidneys as the basis of prerenal azotemia is in excellent accord with the characteristic functional and morphological findings.

(a) *Functional:* The urinary volume is almost always decreased in patients with prerenal azotemia. Often the concentration of the urine is relatively high, although usually it is not as high as would be expected in relation to the volume of the urine were the kidneys functionally intact. Furthermore, the observation can often be made that with the persistence of the oliguria the maximal specific gravity of the urine falls more or less rapidly until it may be fixed close to 1.010. The decreased urinary volume is readily understood as a manifestation of diminished volume of blood flow through the glomeruli. The lessened concentrating ability of the kidneys is doubtless a manifestation of impaired tubular function, which, in the light of the great oxygen consumption of the kidney, is readily comprehensible on the basis of decreased renal blood flow. Likewise, the not uncommon slight albuminuria may well be due to injury to the glomerular membrane as a result of decreased blood flow.

(b) *Morphological:* At necropsy patients with prerenal azotemia may present very little structural alteration in the kidneys. In other cases, however, there are marked regressive changes in the tubular epithelium, which may attain widespread necrosis, rarely with foci of calcification. These changes are readily explained on an ischemic basis; the intensity of the regressive changes presumably largely parallels the degree of the diminution in renal blood flow.

Remarks on Therapy

Time is lacking for detailed discussion of therapy. A few words may be permitted, however, regarding the significance for the course of renal and prerenal azotemia of measures which affect the volume of blood flow through the kidneys.

Restriction of protein in the diet has long been the cornerstone of the management of patients with renal insufficiency, especially when there is nitrogen retention in the blood. The conception underlying protein restriction has been that, since the ability of the kidneys to excrete the nitrogenous end products of protein metabolism is diminished, it is wise to decrease the ingestion of protein to an amount within the capacity of the kidneys to eliminate and thus avert nitrogen retention. In actual practice, however, one often has the impression that, even though rigid restriction of protein in the diet achieves the "laboratory success" of lowering the nonprotein nitrogen of the blood to some extent, the patient becomes weaker and more anemic. In such cases, the addition of protein to the diet is sometimes followed by subjective improvement and rise in the hemoglobin content of the blood. From the point of view of the relation of diet to renal function, there are also experimental observations indicating that in the past protein restriction has often, if not usually, been carried too far in the treatment of renal insufficiency. Jolliffe and Smith showed that dogs have a higher urea clearance when on a high protein diet than when on a low protein diet. This observation has been confirmed by Van Slyke and his coworkers, who found in the dog that the urea clearance may be as low as 15 c.c. per minute on a low protein diet and as high as 90 c.c. per minute on a high protein diet. The latter investigators also showed that the variations in urea clearance brought about by diet parallel variations in blood flow through the kidney. There is excellent experimental evidence to show that a low protein diet tends to lower both the functional accomplishment of the kidneys and the blood flow through these organs. It would appear highly undesirable further to lower blood flow through kidneys in which the circulation is already hindered by such processes as glomerulo-nephritis or arteriolar sclerosis. Theoretically, at least, it thus appears that protracted low protein diet may be undesirable both from the point of view of diminishing the functional accomplishment of the kidneys

and because of the possibility that the progress of the pathological process may be accelerated by decreased renal blood flow. Moreover, most patients with renal disease have at least a tendency to hypoproteinemia, and since Epstein's work it is known that low protein diet may further lower the protein content of the plasma. It would appear that the question of the protein ration in renal insufficiency merits consideration from broader points of view than have generally been adopted in the past. Too often there has been a tendency to regard the functional capacity of the kidney as fixed without considering the great probability that even the severely diseased organ may be able to increase both its functional accomplishment and its blood supply in response to greater demand. Of late years I have become less and less stringent regarding protein restriction and believe that the patients are definitely the better for it.

In patients with prerenal azotemia, the cardinal therapeutic indication is obviously to elevate the decreased circulating blood volume and thereby increase the cardiac output and with it the blood flow through the kidneys. The measure called for is almost always the intravenous injection of the solution best calculated to restore the blood volume in the condition in question. Transfusion of blood is the most useful in shock due to hemorrhage or trauma and may also be very valuable in other forms of peripheral circulatory failure. In almost all forms of prerenal azotemia the use of the intravenous drip of sodium chloride solution with or without glucose is the fundamental therapeutic measure, and one which is often life-saving. In those forms of prerenal azotemia which result from depletion of electrolytes—for example, in vomiting, diabetic coma, and the crises of Addison's disease—the administration of hypertonic sodium chloride solution may lead to quicker improvement than does physiological salt solution. It need hardly be emphasized that when the circulating blood volume is decreased as a result of loss of electrolytes, the administration of hypertonic glucose solutions does not fulfill the therapeutic

indication; sodium chloride must also be given to rebuild the skeleton of electrolytes on which the circulating volume is maintained.

Summary

The primary criterion of impairment of renal function is a concentration of the urine disproportionately low in comparison to the urinary volume.

When impairment of renal function arises from gradually progressive lesions of the kidney, as in most forms of Bright's disease, three stages can usually be differentiated:

1. A latent stage in which the decrease in concentrating ability merely impinges on the large factor of safety of the kidney without repercussion on the organism as a whole.

2. A stage of compensated impairment of renal function in which the decreased concentrating ability is atoned for by increase in urinary volume. There is no retention of potential urinary constituents and the only symptoms and signs are those due to the polyuria.

3. A stage of decompensated impairment of renal function in which the volume of urine is not sufficient to make up for the decreased concentrating ability with resultant retention of potential urinary constituents. The resulting symptoms of uremia are due not only to the direct effects of the retained urinary constituents; the organism also suffers from dehydration and demineralization due partially to regulatory adjustments to maintain the constancy of the internal environment in the face of impaired renal function and partially to gastro-intestinal disturbances.

Impairment of renal function with consequent azotemia and uremia occurs in two great groups of cases:

1. Renal azotemia, in which the impairment of renal function is due to structural changes in the kidneys, e.g., Bright's disease, polycystic kidneys, pyelonephritis, etc.

2. Prerenal azotemia, in which the disturbance in renal function is due to causes not necessarily documented by structural alterations in the kidneys. Available evidence

indicates that the impairment of renal function is most often, if not always, due to diminution in the volume of blood flow through the kidneys, which results in diminution of both urinary volume and concentration. The decrease in renal blood flow is in turn the result, in at least most instances, of diminution in circulating blood volume. So to speak, the prerenal azotemias constitute a chapter in the pathology of the circulation.

On the basis of clinical observations, and in the light of experiments indicating that urea clearance and renal blood flow are affected by the protein ration, it is pointed out that protein restriction has often been carried to disadvantageous degrees in the treatment of renal insufficiency.

AMENDMENT TO THE CONSTITUTION

Presented by Dr. William S. Thomas at Stated Meeting, April 1, 1937
Approved by Council on April 28, 1937
Adopted November 4, 1937

Article 3, Section 5

"After the words, 'other than medical', insert the following: 'or must, in lieu thereof, possess qualifications which are approved by the Council'," the entire Section thus reading:

Section 5. A candidate for election as an Associate must be a graduate of at least five years' standing of a scientific institution other than medical, or must, in lieu thereof, possess qualifications which are approved by the Council, and be engaged in teaching in subjects allied to medicine or hold an official position in a health department, quarantine station or medical library in the United States.

MEMBERS ELECTED

Raul Pietri ..... 501 Grand Ave., Asbury Park, N. J.
Sidney Grossman ..... 1112 Park Avenue
Milton Helpern ..... 1391 Madison Avenue
Earle P. Huff ..... 141 Columbia Heights, Brooklyn
Emerson C. Kelly ..... 269 South Main Avenue, Albany, N. Y.
Herman H. Lardaro ..... 230 East 48 Street
Alfred Lilienfeld ..... 121 East 60 Street
Walter D. Ludlum, Jr. ..... 40 East 61 Street
Robert R. M. McLaughlin ..... 40 East 61 Street
William B. Rawls ..... 430 East 86 Street
Aaron Bell ..... 57 West 57 Street
Claude A. Burrett ..... 1 East 105 Street
Maurice J. Costello ..... 140 East 54 Street
William M. Dick ..... 77 Park Avenue
Ernest Kraft ..... 33 East 61 Street
Samuel W. Lambert, Jr. ..... 955 Lexington Avenue
Joseph S. Lawrence ..... 100 State Street, Albany
Allan J. Roos ..... 115 East 72 Street
Robert C. Schleussner ..... 131 East 91 Street
Henry P. Schugt ..... 30 East 40 Street
Zenas Horace Ellis ..... 58 East 65 Street
Burdge Perine MacLean ..... Huntington, N. Y.
Hyman J. Udinsky ..... 29 Passaic Avenue, Passaic, N. J.
Benzion Liber ..... 611 West 158 Street
Sol Sydney Lichtman ..... 395 Riverside Drive
John F. Mahoney ..... U. S. Marine Hospital, Stapleton, S. I.
T. Campbell Thompson ..... 404 East 55 Street
Byard Williams ..... 140 East 54 Street
Walter Hipp ..... 140 East 54 Street
Robert Lee Patterson, Jr. ..... 135 East 65 Street
Ralph Eugene Swope ..... 667 Madison Avenue
Edward Tolstoi ..... 2 East 94 Street
Theodore P. Wolfe ..... 730 Park Avenue
Charles A. Flood ..... 420 Riverside Drive

PROCEEDINGS OF ACADEMY MEETINGS
NOVEMBER

STATED MEETINGS

November 4

I. Executive Session—a. Reading of the Minutes; b. Election of Members; c. Report of Nominating Committee; d. Vote on Amendment to Constitution.

II. Papers of the Evening—(Tenth Annual Graduate Fortnight)—a. Nature of hypertension, Irvine H. Page, The Lilly Clinical Research Laboratory, Indianapolis, Ind.; b. Clinical aspects of hypertension, including malignant hypertension, Herman O. Mosenthal, Professor of Clinical Medicine, New York Post-Graduate Medical School, Columbia University; c. Evaluation of the surgical treatment of hypertension, George J. Heuer, Professor of Surgery, Cornell University Medical College.

THE HARVEY SOCIETY (in affiliation with the New York Academy of Medicine)

November 18

The Second Harvey Lecture, "The Pasteur-Meyerhof Reaction in Muscle Metabolism," Einar Londsgaard, Institute of Medical Physiology, University of Copenhagen. This lecture took the place of the second Stated Meeting of the Academy for November.

SECTION MEETINGS

The following Sections graciously consented to forego their regular meetings November 1 to 12 in favor of the Tenth Annual Graduate Fortnight: Dermatology and Syphilology, Surgery, Neurology and Psychiatry, Historical and Cultural Medicine, Pediatrics.

Section of Ophthalmology—November 15

I. Instructional Hour (7:00 to 8:00); Embryology, Brittain F. Payne.

II. Slit-Lamp Demonstration—Milton L. Berliner, Wendell L. Hughes, Girolamo Bonaccolto, Gordon M. Bruce.

III. Reading of the Minutes (8:30).

IV. Reading of Report of Standards for Out-Patient Ophthalmologic Service—Conrad Berens.

V. Instruments Demonstrated—A simplified gonioscopic outfit, Isaac Hartshorne.

VI. Presentation of Cases—a. Microphthalmos with cyst formation, Donald W. Bogart (by invitation); b. Coats' disease, Robert M. Oliver (by invitation); c. Conjunctivitis tularensis, David H. Webster; d. Sarcoma of eyelid, Fritz Bloch (by invitation).

VII. Paper of the Evening—Choroidal sclerosis in coronary arteriosclerosis, Martin Cohen; Discussion: James R. Lisa, Robert H. Halsey.

Section of Medicine—November 16

I. Reading of the Minutes.

II. Paper of the Evening—Recent clinical and experimental advances in cancer research, with reference to heredity, biology, and chemistry, Francis Carter Wood.

III. Discussion—a. Carcinogenic chemicals, S. Burt Wolbach, Boston (by invitation); b. Cell potencies and the relation of certain intracellular compounds to growth, Stanley P. Reimann, Philadelphia (by invitation); c. The importance of statistical analysis in medicine and experimental research, Wilhelmina Dunning (by invitation).

IV. General Discussion.

JOINT MEETING OF THE SECTION OF NEUROLOGY AND PSYCHIATRY AND NEW YORK NEUROLOGICAL SOCIETY—November 16

I. PAPERS OF THE EVENING—a. Mental changes in chorea minor, Donald Shaskan (by invitation); Discussion: Karl M. Bowman (by invitation), S. Bernard Wortis, Israel Wechsler, David Arbuse; b. Cerebral lesions due to vasomotor disturbances following brain trauma, Max Helfand (by invitation); Discussion: Charles Davison, Armando Ferraro, Lewis Stevenson, Foster Kennedy, Richard Brickner; c. Oxycephaly. A new operation, result. A preliminary report, Joseph E. J. King; Discussion: Foster Kennedy, S. Bernard Wortis, Ira Cohen, George Hyslop; d. Subdural hematoma, acute and chronic, with some remarks about treatment, Abraham Kaplan; Discussion: Foster Kennedy, Ira Cohen, Joseph E. King.

II. EXECUTIVE SESSION.

SECTION OF OTOLARYNGOLOGY—November 17

I. READING OF THE MINUTES.

II. PAPER OF THE EVENING—Curable cases of meningitis, Wells P. Eagleton.

III. DISCUSSION—a. From the clinical standpoint, Isidore Friesner, Josephine B. Neal, James G. Dwyer; b. From the pathological standpoint, Joseph G. Druss, Andrew A. Eggston.

IV. GENERAL DISCUSSION.

V. EXECUTIVE SESSION.

SECTION OF GENITO-URINARY SURGERY—November 17

The Section decided to forego its November meeting, inasmuch as the whole of the second week of the Fortnight was given over to urologic subjects.

JOINT MEETING OF THE SECTION OF ORTHOPEDIC SURGERY AND THE PHILADELPHIA ORTHOPEDIC CLUB—November 19

I. READING OF THE MINUTES.

II. PRESENTATION OF CASES—a. Fracture of the neck of the femur treated by the ambulatory method, Samuel Kleinberg, Max Rabinowitz (by invitation); b. Osteochondroma of the epiphyseal plate of the knee joint, Harry Finkelstein; c. Partial resection of the ischium for tuberculosis, Henry Milch; d. Muscle angiomata, diagnosed and treated by venography and injection, I. Tunick (by invitation), M. Pomeranz (by invitation); e. Milroy's disease, Edgar Oppenheimer; f. Complete anterior dislocation of the cervical vertebrae, with contusion of the spinal cord, quadruplegia and recovery, Donald E. McKenna; g. Some observations on the embryology of the hip joint, Paul C. Colonna, D. A. DeSanto (by invitation); h. Fascial transplant for paralysis of abdominal muscles, Leo Mayer; i. Three cases from St. Luke's Orthopedic Clinic to illustrate a simple exploratory incision of the knee joint, Mather Cleveland, David M. Bosworth.

III. PAPERS OF THE AFTERNOON—a. An encircling fascial band operation for hallux valgus and splay foot, Arthur Krida; b. Use of metal bone plates in orthopedic surgery, M. Beckett Howorth; c. Pre-adolescent wedging round back treated by spine fusion operations. End result study of sixty cases, Leon Lantzounis; d. A standard of anteroposterior alignment of the lumbosacral joint, with deductions concerning development and displacement, Albert B. Ferguson (by invitation); e. Summary of results of 1935 epidemic of poliomyelitis, Charlton Wallace; f. Resume of eighty operative cases of internal derangement of the knee joint, limited to damage to the semilunar cartilages, William Hadden Irish.

IV. GENERAL DISCUSSION.

V. EXECUTIVE SESSION.

SECTION OF OBSTETRICS AND GYNECOLOGY—November 23

From The Margaret Hague Maternity Hospital, Jersey City

I. CASE REPORT—Aplastic anemia in a case of streptococcic puerperal sepsis treated with sulfanilamide, James F. Norton (by invitation), Nicholas M. Alter (by invitation); Discussion: Cornelius P. Rhoads.

II. PAPERS OF THE EVENING—a. Roentgen diagnosis of placenta previa, Milton A. Carvalho (by invitation), John A. McGeary (by invitation); Discussion: Howard C. Moloy; b. Efficiency of sodium lactate in raising carbon dioxide combining power, Leon C. Chesley (by invitation), Felix W. Vann (by invitation); Discussion: Samuel A. Cosgrove.

AFFILIATED SOCIETIES

NEW YORK ROENTGEN SOCIETY—(IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE)—November 15

I. PRESENTATION OF INTERESTING CASES.

II. SUBTRACTION PLANIGRAPHY AND SERIESCOPY—B. G. Ziedses Des Plantes.

III. EXECUTIVE SESSION.

NEW YORK MEETING OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE

November 17

I. Differences in the spread of dye in the skin of normal and tuberculous guinea pigs, A. L. Joyner (by invitation), F. R. Sabin.

II. The application of vital dyes to the study of sheath cell origin, S. R. Detwiler.

III. Assay of thyrotropic hormone on day old chicks, G. K. Smelser (Introduced by P. E. Smith).

IV. The effect of testosterone propionate upon the gonadotropic hormone excretion and vaginal smears of a human female castrate, Udall J. Salmon (Introduced by R. T. Frank).

V. Treatment of hepathomegaly in juvenile diabetes mellitus with a pancreatic extract, Leo S. Radwin (Introduced by B. Kramer).

VI. The liver lipids and fecal excretion of fat and nitrogen in dogs with ligated pancreatic ducts, Elaine P. Ralli, Saul H. Rubin (by invitation), Clara H. Present (by invitation).

VII. Serum phosphatase activity in generalized osteosclerosis, Kaj Roholm (by invitation), Alexander B. Gutman, Ethel B. Gutman (by invitation).

NEW YORK PATHOLOGICAL SOCIETY—(IN AFFILIATION WITH THE NEW YORK ACADEMY OF MEDICINE)—November 18

I. CASE REPORTS—a. Actinomycosis of the ovary, Lionel S. Auster; b. Papilloma choroideum of the fourth ventricle, Andrea Saccone, Abraham Rosenthal; c. Large solitary cyst of the pineal gland, Amour F. Liber.

II. PAPERS OF THE EVENING—a. A study of the pharyngeal pituitary gland, R. H. Melchionna (by invitation); b. Pathological changes of the heart in sudden death, James R. Lisa.

III. EXECUTIVE SESSION.

DEATHS OF FELLOWS OF THE ACADEMY

FERRIS, ALBERT WARREN, 111 North Walnut Street, East Orange, New Jersey: born in Brooklyn, New York, December 3, 1856; died in East Orange, New Jersey, October 4, 1937; received from New York University the degrees of A.B. in 1878 and A.M. in 1885; graduated in medicine from the College of Physicians and Surgeons in 1882; elected a Fellow of the Academy January 15, 1891.

Dr. Ferris was president of the New York State Commission in Lunacy from 1907 to 1911 and Director of Saratoga Springs State Reservation Commission from 1913 to 1916. He was at one time Consulting Physician to Manhattan and Binghamton State Hospitals.

Dr. Ferris was a member of the American Congress on Internal Medicine, the American Medical Association, the New York State Medical Society, and a Fellow of the American College of Physicians.

O'CONNOR, FRANCIS WILLIAM, 50 Haven Avenue, New York City: born in Limerick, Ireland, May 13, 1884; died in New York City, October 3, 1937; graduated in medicine from St. Bartholomew's Hospital and College, London, in 1907, and the Royal College of Physicians in 1913; elected a Non-Resident Fellow of the Academy November 6, 1930.

Early in his career Dr. O'Connor made the study of tropical disease his specialty, spending several years in field and hospital research in South Africa. In 1913 Cambridge University awarded him the degree of Doctor of Tropical Medicine. He came to the United States in 1923 and for a time was associated with the Rockefeller Institute.

At the time of his death, Dr. O'Connor was Associate Professor of Medicine at the College of Physicians and Surgeons and Associate Attending Physician to the Presbyterian Hospital.

Dr. O'Connor was a member of the Royal College of Surgeons.

TOUSEY, SINCLAIR, Garden City, New York: born in Brooklyn, New York, December 19, 1864; died in Whitefield, New Hampshire, September 25, 1937; received the degrees of A.B. from the Polytechnic Institute of Brooklyn in 1884 and M.A. from Columbia University in 1885; graduated in medicine from the College of Physicians and Surgeons in 1888; elected a Fellow of the Academy April 4, 1895.

INDEX, 1937

A

Abdominal surgery, Further studies on the intraperitoneal use of bovine amniotic fluid in (abstract), J. R. Gepfert and M. L. Stone, 296

Academy, Recent activities of The New York, E. H. Pool, 110

Academy meetings, Proceedings of, 43, 93, 141, 305, 371, 734

—— scholarships, The, 295

Accessions to the Library, Recent, 40, 90, 138, 297, 369, 433, 493, 546, 603, 656

Acetylcholine, Transmission of nervous effects by, Sir Henry Dale, 379

Acid allurate used as an analgesic in 101 cases at Woman's Hospital, Clinical study of (abstract), W. A. Graham and M. De W. Pettit, 492

Adair, Robin and John, Archibald Malloch, 576

Admission, Committee on, 1936, 148

—— , —— —, Report of the, 175

Advertising policy, Change in, 10

Affiliated Societies, Officers of Sections and, 1936, 149

Amberson, J. Burns, Jr., Significance of pregnancy for the tuberculous woman (abstract), 37

Amendment to the Constitution, 732

"American Medicine," Review of, 422

Amniotic fluid in abdominal surgery, Further studies on the intraperitoneal use of bovine (abstract), J. R. Gepfert and M. L. Stone, 296

Anemia from the clinical standpoint, Modern concepts of, E. B. Krumbhaar, 501

Anniversary Discourse, The profession in world turmoil, J. G. Rogers, 47

Annual Meeting of the Academy, January 7, 1937

Address of the Incoming President, J. A. Miller, 118

—— of the Retiring President, E. H. Pool, 110

Medicine and the State, T. D. Thacher, 127

Reports of the Council, Board of Trustees, Committees of the Academy, Annual Report for 1936, April number, 146-239

Arabia, Medical explorers of, Iago Galdston, 512

Azotemia and the pathology of renal blood flow, Prerenal, A. M. Fishberg, 710

B

Bearing of the results of recent studies in nutrition on health and on length of life, H. C. Sherman, 311

Bed for sick and needy physicians, Hosack, 239

Bequests, form of, 239

Biggs (Hermann Michael) Memorial Lecture, Bearing of the results of recent studies in nutrition on health and on length of life, H. C. Sherman, 311

Blood loss during the third stage of labor, Significance of the (abstract), J. B. Pastore, 85

Breech, Management of (abstract) H. C. Williamson, 85

Brunner, Endre K., Bertram G. Smith and, Histologic diagnosis of pregnancy (abstract), 296
Bysshe, Stanley M., Significance of Clostridium Welchü in the genital tract of pregnant and puerperal women (abstract), 491

C

Cagliostro (Count)—an excursion into eighteenth century charlatanism, G. H. Lathrope, 466
Cardiac functional capacity as an aid to prognosis during pregnancy (abstract), H. E. B. Pardee, 38
Cary, William H., Evaluation of male fertilization (abstract), 86
Caughey, J. L., Jr.: A case of pericarditis with effusion, 1
Charlatanism, Count Cagliostro, an excursion into eighteenth century, G. H. Lathrope, 466
Chemical warfare as developed during the World War—probable future development, Adelno Gibson, 397
Chicago city-wide plan for the care of premature infants (abstract), J. H. Hess, 137
Clinical study of acid allurate used as an analgesic in 101 cases at Woman's Hospital (abstract), W. A. Graham and M. De W. Pettit, 492
Clostridium Welchii, in the genital tract of pregnant and puerperal women, Significance of (abstract), S. M. Bysshe, 491
Committees of the Academy, annual reports
Committee on Admission, 175
—— — Fellowship, 175
—— — Library, 176
—— — Medical Education, 220
—— — Public Health Relations, 201
—— — Sections, 226
Appointed annually, 151
Standing, 148
Community provision for the serum treatment of pneumococcic pneumonias, 557
Constitution, Amendment to the, 732
Control of excitation in the nervous system, H. S. Gasser, 324
Correction, 136
Council, Report of the, 153
Course, conduct and complications of labor among physicians' wives (abstract), R. D. Mussey, John Faber, 366
Crane, Norman F. and John F. Deitrick, Harold J. Stewart, Recurrent pericardial effusion of unknown etiology, 11

D

Dale (Sir) Henry, Transmission of nervous effects by acetylcholine, 379
Deafness from otosclerosis, Factual background for the treatment of progressive, E. P. Fowler, 667
—— — —— , New technique in the surgical treatment of severe and progressive, M. Sourdille, 673

Deaths of Fellows and Associate Fellows, 45, 96, 143, 308, 376, 437, 496, 549, 661, 737
Benedict, Stanley Rossiter (Associate), 45
Bierhoff, Frederic, 549
Blake, Joseph Augustus, 549
Brownlee, Harris Fenton (Associate), 143
Ferris, Albert W., 737
Finley, Caroline Sandford, 45
Fox, George Henry, 376
Goldenberg, Hermann, 308
Gould, Everett Willoughby, 550
Gross, Louis, 661
Holden, Ward Andrews, 96
Hunt, J. Ramsay, 550
Jarecky, Herman, 308
Kindred, John Joseph, 661
McCreery, Forbes, Robert, 437
MacHale, Ferdinand Stanislaus, 143
Mandel, Arthur Rudolph, 143
Meierhof, Edward Lee, 662
Mial, Leonidas Le May, 550
Morris, Lewis Rutherford, 46
Myles, Robert Cunningham, 46
O'Connor, Francis William, 737
Pierson, Samuel, 376
Pollitzer, Sigmund, 662
Roberts, Percy Willard, 662
Root, Edward King, 550
Spies, Edwin Albert, 308
Steiner, Joseph Manning, 96
Thornley, Joseph Payne, 496
Tousey, Sinclair, 737
Tracy, William Dwight (Associate), 144
Van Wagenen, Cornelius Doremus, 144
Warren, Luther Fiske, 96
Wiener, Richard George, 144
Wyckoff, John Henry, 376

Deitrick, John F., Harold J. Stewart, Norman F. Crane and, Recurrent pericardial effusion of unknown etiology, 11

Diversa, Joseph A. Hirsheimer, Derrick January and, X-Ray study of gastric function during labor (abstract), 490

Douglas, R. Gordon, Hypertension, chronic nephritis and the toxemias of pregnancy (abstract), 39
—— , — —— , Prevention and control of puerperal infection due to the beta hemolytic streptococcus (abstract), 84

E

Eastman, Nicholson J., Heart disease from the viewpoint of the obstetrician (abstract), 39
Effusion, A case of pericarditis with, J. L. Caughey, Jr., 1
—— of unknown etiology, Recurrent pericardial, H. J. Stewart, N. F. Crane, J. E. Deitrick, 11
Elderly primiparae (abstract), C. R. Tew and K. Kuder, 491
Epstein, Albert A., The nephroses, 621
Ergot preparations in the control of postpartum bleeding, Observations on the relative efficiency of two types of (abstract) R. C. ter Kuile, 489
Erythroblastosis fetalis as a cause of infantile mortality (abstract), C. T. Javert, 84
Evaluation of male fertility (abstract), W. H. Cary, 86
—— of the surgical treatment of hypertension, G. J. Heuer, 692

F

Faber, John, R. D. Mussey and, Course, conduct, and complications of labor among physicians' wives (abstract), 366
Factual background for the treatment of progressive deafness from otosclerosis, E. P. Fowler, 667
Fellows, Associate, Resignation in 1936, 237
—— , Honorary, elected in 1936, 236
—— , Resignations in 1936, 237
Fellowship, Committee on, 1936, 148
—— , —— —, Report of the, 175
Fellowships, Discontinued, 238
Fertility, Evaluation of male (abstract), W. H. Cary, 86
First aid, Medical problem in, R. H. Kennedy, 61
Fishberg, Arthur M., Prerenal azotemia and the pathology of renal blood flow, 710
Fowler, Edmund Prince, Factual background for the treatment of progressive deafness from otosclerosis, 667
Friday Afternoon Lectures, twelfth series, 608
Functions of the hypothalamus, Some, S. W. Ranson, 241
Further studies on the intraperitoneal use of bovine amniotic fluid in abdominal surgery (abstract), J. R. Gepfert and M. L. Stone, 296

G

Galdston, Iago, Medical explorers of Arabia, 512
Gasser, Herbert S., Control of excitation in the nervous system, 324
Gastric function during labor, X-Ray study of (abstract), A. Hirsheimer, D. January and J. Diversa, 490

Gepfert, J. Randolph and Melvin L. Stone, Further studies on the intraperitoneal use of bovine amniotic fluid in abdominal surgery (abstract), 296

Gibson, (Col.) Adelno, Chemical warfare as developed during the World War—probable future development, 397

Graduate Fortnight, Ninth Annual

—— —— , — Chemical warfare as developed during the World War—probable future development, Adelno Gibson, 397

—— —— , — Medical problem in first aid, R. H. Kennedy, 61

—— —— , Tenth Annual, 309, 377

—— —— , — Address of welcome, J. A. Miller, 619

—— —— , — Evaluation of the surgical treatment of hypertension, G. J. Heuer, 692

—— —— , — Nature of hypertension, I. H. Page, 645

—— —— , — Nephroses (The), A. A. Epstein, 621

—— —— , — Prerenal azotemia and the pathology of renal blood flow, A. M. Fishberg, 710

Graham, William A. and Mary DeWitt Pettit, Clinical study of acid allurate used as an analgesic in 101 cases at Woman's Hospital (abstract), 492

Gynecology from the public health viewpoint, Obstetrics and (abstract), J. L. Rice, 366

—— from the viewpoint of the Medical Examiner, Obstetrics and (abstract), H. S. Martland, 367

H

Health and on length of life, Bearing of the results of recent studies in nutrition on, H. C. Sherman, 311

—— Organization of the League of Nations, Scientific work of the, Thorvald Madsen, 439

Heart disease from the viewpoint of the obstetrician (abstract), N. J. Eastman, 39

Hess, Julius H., Chicago city-wide plan for the care of premature infants (abstract), 137

Heuer, George J., Evaluation of the surgical treatment of hypertension, 692

Hirsheimer, A., Derrick January and Joseph Diversa, X-Ray study of gastric function during labor (abstract), 490

Histologic diagnosis of pregnancy (abstract), B. G. Smith and E. K. Brunner, 296

Hosack Bed for sick and needy physicians, 239

Hospital demonstrations in the modern methods of diagnosis and treatment of syphilis, Schedule of lectures and, 36

Hunt, J. Ramsay, Committee on Library Minute on the death of, 655

Hutchinson, Jonathan: the last of the multispecialists, G. M. Bruce, 539

Hydrogen, Investigation of intermediary metabolism with the aid of heavy, Rudolf Schoenheimer, 272

Hypertension, Evaluation of the surgical treatment of, G. J. Heuer, 692
——— , Nature of, I. H. Page, 645
——— , chronic nephritis and the toxemias of pregnancy, viewpoint of the internist (abstract), A. J. B. Tillman, 39
——— , ——— ——— , viewpoint of the obstetrician (abstract), R. G. Douglas, 39
Hypoglycemic therapy of the psychoses, Origin and nature of the, Manfred Sakel, 97
Hypothalamus, Some functions of the, S. W. Ranson, 241

I

Ideals in medicine, J. A. Miller, 118
Infantile mortality, Erythroblastosis fetalis as a cause of (abstract), C. T. Javert, 84
Intermediary metabolism with the aid of heavy hydrogen, Investigation of, Rudolf Schoenheimer, 272
Intracranial injury in the premature infant, Relation of labor to (abstract), W. E. Studdiford, H. P. Salter, 137
Investigation of intermediary metabolism with the aid of heavy hydrogen, Rudolf Schoenheimer, 272

J

January, Derrick, and Joseph Diversa, A. Hirsheimer, X-Ray study of gastric function during labor (abstract), 490
Javert, Carl T., Erythroblastosis fetalis as a cause of infantile mortality (abstract), 84

K

Kennedy, Robert H., Medical problem in first aid, 61
Krumbhaar, E. B., Modern concepts of anemia from the clinical standpoint, 501
Kuder, K., Cloyce R. Tew and, Elderly primiparae (abstract), 491

L

Labate, John S., Skin hyperesthesia in acute salpingitis (abstract), 489
Labor among physicians' wives, course, conduct and complications of (abstract), R. D. Mussey, John Faber, 366
— , Significance of the blood loss during the third stage of (abstract), J. B. Pastore, 85
— , X-Ray study of gastric function during (abstract), 490
Laity, Lectures to the, third series, 614
Lathrope, George H., Count Cagliostro—an excursion into eighteenth century charlatanism, 466
League of Nations, Scientific work of the Health Organization of the, Thorvald Madsen, 439
Lectures and hospital demonstrations in the modern methods of the diagnosis and treatment of syphilis, Schedule of, 36
—— , Thomas William Salmon Memorial, 117
—— to the Laity, third series, 614

Library, Committee on, 1936, 148
—— , ——— —, Minute on the death of J. Ramsay Hunt, 655
—— , ——— —, Report of the, 176
—— funds, donations to the, 239
—— notes, Death of Mr. Leonard Mackall, Archibald Malloch, 428
—— — , J. Ramsay Hunt, 655
—— — , Wanted by the Library, 87
Library, Recent Accessions to the, 40, 90, 138, 297, 369, 433, 493, 546, 603, 656
—— , selected list of periodicals added in 1936, 87
Luetic Antepartum Clinic at Bellevue Hospital, Results of therapy in the (abstract), M. D. Speiser, 297

M

Mackall, Leonard L., Death of, Archibald Malloch, 428
Madsen, Thorvald, Scientific work of the Health Organization of the League of Nations, 439
Malloch, Archibald, Death of Mr. Leonard L. Mackall, 428
—— , —— , Robin and John Adair, 576
Management of breech (abstract), H. C. Williamson, 85
Martland, Harrison S., Obstetrics and gynecology from the viewpoint of the Medical Examiner (abstract), 367
Maternal mortality rates in the United States, Postgraduate medical education with especial reference to the present, 597
Matthews, Harvey B., Tuberculosis from the point of view of the obstetrician (abstract), 37
Medical Education, Committee on, 1936, 148
—— ——— , ——— —, Report of the, 220
—— Examiner, Obstetrics and gynecology from the viewpoint of the (abstract), H. S. Martland, 367
—— explorers of Arabia, Iago Galdston, 512
—— Information Bureau, Report of the, 227
—— problem in first aid, R. H. Kennedy, 61
Medicine and the State, T. D. Thacher, 127
—— , Ideals in, J. A. Miller, 118
Meetings at the Academy, Report of offices and, 234
Members, elected 1937, 304, 368, 733
—— , Non-Resident, elected in 1936, 237
—— , Resident, elected in 1936, 236
—— , —— , transferred to Non-Resident, 237
Membership roster, Changes in, 236
Miller, James Alexander, Address of welcome to the Tenth Annual Graduate Fortnight, 619
——, — ——— , Ideals in medicine, Address of the Incoming President, 118
Modern concepts of anemia from the clinical standpoint, E. B. Krumbhaar, 501

Multispecialists, Jonathan Hutchinson, the last of the, G. M. Bruce, 539
Mussey, R. D. and Faber, John, Course, conduct, and complications of labor among physicians' wives (abstract), 366

N

Nature of hypertension, I. H. Page, 645
Nephritis and the toxemias of pregnancy, Hypertension, chronic, viewpoint of the internist (abstract), A. J. B. Tillman, 39
——— — — ——— , viewpoint of the obstetrician, (abstract), R. G. Douglas, 39
Nephroses, The, A. A. Epstein, 621
Nervous effects by acetylcholine, Transmission of, Sir Henry Dale, 379
—— system, Control of excitation in the, H. S. Gasser, 324
New technique in the surgical treatment of severe and progressive deafness from otosclerosis, M. Sourdille, 673
New York Academy of Medicine, Recent activities of The, E. H. Pool, 110
Notes
Donations to the Library funds, 239
Form of bequests, 239
Hosack Bed for sick and needy physicians, 239
Nutrition on health and on length of life, Bearing of the results of recent studies in, H. C. Sherman, 311

O

Obituary, 1936, 238
Observations on the relative efficiency of two types of ergot preparations in the control of postpartum bleeding (abstract), R. C. ter Kuile, 489
Obstetrician, Heart disease from the viewpoint of the (abstract), N. J. Eastman, 39
——— , Tuberculosis from the point of view of the (abstract), H. B. Matthews, 37
Obstetrics and gynecology from the public health viewpoint (abstract), J. L. Rice, 366
—— — ——— from the viewpoint of the Medical Examiner (abstract), H. S. Martland, 367
Officers of Sections and Affiliated Societies, 1936, 149
—— and Staff of the Academy, 146
Offices and meetings at the Academy, Report of, 234
Origin and nature of the hypoglycemic therapy of the psychoses, Manfred Sakel, 97
Otosclerosis, Factual background for the treatment of progressive deafness from, E. P. Fowler, 667
——— , new technique in the surgical treatment of severe and progressive deafness from, M. Sourdille, 673

P

Page, Irvine H., Nature of hypertension, 645
Pardee, Harold E. B., Cardiac functional capacity as an aid to prognosis during pregnancy (abstract), 38
Pastore, John B., Significance of the blood loss during the third stage of labor (abstract), 85
Pericardial effusion of unknown etiology, Recurrent, H. J. Stewart, N. F. Crane, J. E. Deitrick, 11
Pericarditis with effusion, A case of, J. L. Caughey, Jr., 1
Periodicals, A selected list of, added in 1936, 87
Pettit, Mary DeWitt, William A. Graham and, Clinical study of acid allurate used as an analgesic in 101 cases at Woman's Hospital (abstract), 492
Philadelphia County Medical Society, Annual Postgraduate Institute of the, 109
Physicians, Hosack Bed for sick and needy, 239
Physicians' wives, course, conduct, and complications of labor among (abstract), R. D. Mussey, John Faber, 366
Pneumococcic pneumonias, Community provision for the serum treatment of, 557
Pool, Eugene H., Recent activities of The New York Academy of Medicine, Address of the Retiring President, 110
Postgraduate Institute of the Philadelphia County Medical Society, Annual, 109
——— medical education—with especial reference to present maternal mortality rates in the United States, 597
Postpartum bleeding, Observations on the relative efficiency of two types of ergot preparations in the control of (abstract), R. C. ter Kuile, 489
Pregnancy, Cardiac functional capacity as an aid to prognosis during (abstract), H. E. B. Pardee, 38
——— , Histological diagnosis of (abstract), B. G. Smith and E. K. Brunner, 296
——— for the tuberculous woman, Significance of (abstract), J. Burns Amberson, Jr., 37
Premature infant, Relation of labor to intracranial injury in the (abstract), W. E. Studdiford, Hiram P. Salter, 137
—— infants, Chicago city-wide plan for the care of (abstract), J. H. Hess, 137
Prerenal azotemia and the pathology of renal blood flow, G. J. Heuer, 692
Prevention and control of puerperal infection due to the beta hemolytic streptococcus (abstract), R. G. Douglas, 84
Primiparae, Elderly (abstract), C. R. Tew and K. Kuder, 491
Proceedings of Academy Meetings, 43, 93, 141, 305, 371, 734
Professions in world turmoil, Anniversary discourse, J. G. Rogers, 47
Psychoses, Origin and nature of the hypoglycemic therapy of the, Manfred Sakel, 97

Public Health Relations, Committee on, 1936, 148
— — —— , ——— —, Report of Activities for 1936, 201
— — —— , ——— —, Report of special subcommittee on community provision for the serum treatment of pneumococcic pneumonias, 557
Public health viewpoint, Obstetrics and gynecology from the (abstract), J. L. Rice, 366
Puerperal infection due to the beta hemolytic streptococcus, Prevention and control of (abstract), R. G. Douglas, 84

R

Rabelais as a physician, F. T. van Beuren, Jr., 349
Ranson, S. W., Some functions of the hypothalamus, 241
Recent Accessions to the Library, 40, 90, 138, 297, 369, 433, 493, 546, 603, 656
— activities of The New York Academy of Medicine, E. H. Pool, 110
Recurrent pericardial effusion of unknown etiology, H. J. Stewart, N. F. Crane, J. E. Deitrick, 11
Relation of labor to intracranial injury in the premature infant (abstract), W. E. Studdiford, H. P. Salter, 137
Renal blood flow, Prerenal azotemia and the pathology of, A. M. Fishberg, 710
Resignations in 1936, 237
Results of therapy in the Luetic Antepartum Clinic at Bellevue Hospital (abstract), M. D. Speiser, 297
Rice, John L., Obstetrics and gynecology from the public health viewpoint (abstract), 366
Robin and John Adair, Archibald Malloch, 576
Rogers, James Grafton, The professions in world turmoil, Anniversary discourse, 47

S

Sakel, Manfred, Origin and nature of the hypoglycemic therapy of the psychoses, 97
Salmon (Thomas William) Memorial Lectures, 117
Salpingitis, Skin hyperesthesia in acute (abstract), J. S. Labate, 489
Salter, Hiram P., William E. Studdiford, Relation of labor to intracranial injury in the premature infant (abstract), 137
Schedule of lectures and hospital demonstrations in the modern methods of diagnosis and treatment of syphilis, 36
Schoenheimer, Rudolf, Investigation of intermediary metabolism with the aid of heavy hydrogen, 272
Scholarship, The Academy, 295
Scientific work of the Health Organization of the League of Nations, Thorvald Madsen, 439

Sections and Affiliated Societies, Officers of, 1926, 149
—— , Committee on 1936, 148
—— , ——— —, Report of the, 226
—— , Members of Advisory Committees on, 1936, 150
Serum treatment of pneumococcic pneumonias, Community provision for, 557
Sherman, Henry C., Bearing of the results of recent studies in nutrition on health and on length of life, 311
Significance of the blood loss during the third stage of labor (abstract), J. B. Pastore, 85
——— of Clostridium Welchii in the genital tract of pregnant and puerperal women (abstract), S. M. Bysshe, 491
——— of pregnancy for the tuberculous woman (abstract), J. Burns Amberson, Jr., 37
Skin hyperesthesia in acute salpingitis (abstract), J. S. Labate, 489
Smith, Bertram G. and Endre K. Brunner, Histologic diagnosis of pregnancy (abstract), 296
Sourdille, Maurice, New technique in the surgical treatment of severe and progressive deafness from otosclerosis, 673
Speiser, Mortimer D., Results of therapy in the Luetic Antepartum Clinic at Bellevue Hospital (abstract), 297
Staff of the Academy, Officers and, 146
— — — —— , Partial list of, 147
State, Medicine and the, T. D. Thacher, 127
Stewart, Harold J., Norman F. Crane and John E. Deitrick, Recurrent pericardial effusion of unknown etiology, 11
Stone, Melvin L., J. Randolph Gepfert and, Further studies on the intraperitoneal use of bovine amniotic fluid in abdominal surgery (abstract), 296
Streptococcus, Prevention and control of puerperal infection due to the beta hemolytic (abstract), R. G. Douglas, 84
Studdiford, William E., Hiram P. Salter, Relation of labor to intracranial injury in the premature infant (abstract), 137
Syphilis, Schedule of lectures and hospital demonstrations in the modern methods of diagnosis and treatment of, 36

T

ter Kuile, Roger C., Observations on the relative efficiency of two types of ergot preparations in the control of postpartum bleeding (abstract), 489
Tew, Cloyce R. and K. Kuder, Elderly primiparae (abstract), 491
Thacher, Thomas D., Medicine and the State, 127
Tillman, Alvin J. B., Hypertension, chronic nephritis and the toxemias of pregnancy (abstract), 39

Toxemias of pregnancy, Hypertension, chronic nephritis and the, viewpoint of the internist (abstract), A. J. B. Tillman, 39

—— — ——— , viewpoint of the obstetrician (abstract), R. G. Douglas, 39

Transmission of nervous effects by acetylcholine, Sir Henry Dale, 379

Treasurer, Abstract of Report, 170

Trustees, Board of, 1936, 146

—— , — —, Report of the, 165

Tuberculosis from the point of view of the obstetrician (abstract), H. B. Matthews, 37

Tuberculous woman, Significance of pregnancy for the (abstract), J. Burns Amberson, Jr., 37

V

van Beuren, Frederick T., Jr., Rabelais as a physician, 349

W

Williamson, Hervey C., Management of breech (abstract), 85

World turmoil, The professions in, Anniversary discourse, J. G. Rogers, 47

— War, Chemical warfare as developed during the, —probable future development, Adelno Gibson, 397

X

X-Ray study of gastric function during labor (abstract), A. Hirsheimer, D. January and J. Diversa, 490

MEMBERS OF
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In discussing the treatment of decomposition, Feer says: "The period of repair may be shortened by giving suitable additional food; the best, probably, being buttermilk to which carefully regulated proportions of dextrin and maltose preparations or malt soup are added."—*E. Feer: Text-Book of Pediatrics, J. B. Lippincott Co., Phila., 1922, p. 284.*

In the treatment of infantile atrophy, Fischer recommends the following: "The carbohydrate should be increased by gradual addition of dextrimaltose.

"Malt soup or dextrimaltose (Mend's) should be added in teaspoonful or more doses to each feeding until the point of carbohydrate tolerance is reached."—*L. Fischer: Diseases of Infancy and Childhood, F. A. Davis Co., Phila., 1925, V. 1, p. 285.*

Grulee, discussing treatment of decomposition, observes: "As a rule it is best to start with 2 to 2½ or 3 ounces of albumin milk to the pound weight in 24 hours; the sugar to be added is in the form of a maltose-dextrin mixture. One should never delay too long in adding this."—*C. G. Grulee: Infant Feeding, W. B. Saunders Co., Phila., 1922, p. 265.*

Referring to the hypotrophic infant, Herrman writes: "In mild cases, the addition of dextrimaltose instead of cane or milk sugar may be sufficient to obtain a gain in weight."—*C. Herrman: The treatment of nutritional disorders in artificially-fed infants, New York M. J. 114:158-160, August, 1921.*

In discussing artificial feeding in athrepsia, Hess states: "The carbohydrates are usually added in a slowly fermentable form, such as the maltose and dextrin compounds, which are usually started by the addition of four grams per kilogram (1/15 ounce per pound) and increased until eight grams or more per kilogram (¼ ounce per pound) of body weight are added."—*J. H. Hess: Feeding and the Nutritional Disorders in Infancy and Childhood, F. A. Davis Co., Phila., 1928, p. 278.*

Concerning the treatment of marasmus, Hill says: "When the stools have become smooth and salve-like, carbohydrate, in the form of dextrimaltose, may be gradually added up to the limit of tolerance."—*L. W. Hill: Practical Infant Feeding, W. B. Saunders Co., Phila., 1922, p. 281.*

"A spasmophilic baby on bottle feeding should receive a limited amount of milk—a pint, or at the most 24 ounces in the 24 hours—to which cereal gruel and some form of sugar is added, preferably one of the malt dextrin preparations; also the early addition of other foods than milk to the baby's diet."—*M. Jampolis: Infantile spasmophilia, Interstate M. J. 25:652, Sept., 1918; abst. Arch. Pediat. 35:691, Nov. 1918.*

With reference to the treatment of diarrhea, Lust writes: "After several days, 2% to 3% of a maltose-dextrin preparation may be added (Dextri-Maltose). This is preferable to the easily fermentable lactose or cane sugar."—*F. Lust: The Treatment of Children's Diseases, J. P. Lippincott Co., Phila., 1930, p. 145.*

"The treatment of artificially fed children in the first of these groups consists in putting them on a low fat dietary, and giving them carbohydrate in the form of one of the less fermentable sugars—e.g., dextrimaltose."—*L. G. Parsons: Wasting disorders of early infancy, Lancet, 1:687-694, April 5, 1924.*

Pearson and Wyllie in discussing the treatment of milder cases of inanition say: "Regulation of this disturbed organismal balance is obtained by the addition of carbohydrates, while fat and casein are reduced. For this purpose dextrimaltose and flour are better than the ordinary sugars, since they are more slowly absorbed and have greater efficacy in their powers of controlling the flora in the large intestine."—*W. J. Pearson, and W. G. Wyllie: Recent Advances in Diseases of Children, P. Blakiston's Son & Co., Phila., 1930, p. 116.*

Regarding the treatment of the marantic infant, Raue states: "After the intolerance to sugar has been overcome a carbohydrate, preferably Dextrimaltose, may be added."—*C. S. Raue: Diseases of Children, Boericke & Tafel, Phila., 1922, p. 427.*

In discussing the treatment of atrophy, Thursfield and Paterson, state: "If the baby continues to improve, the next step in the treatment is to add to the milk one of the less fermentable carbohydrates, such as dextrimaltose; . . ."—*H. Thursfield, and D. Paterson: Diseases of Children, William Wood & Co., 1929, p. 105.*

"I also find dextrin-maltose an excellent addition to albumin-milk when the first object of that food has been achieved and a gain in weight is desired; in this way I have succeeded in feeding albumin-milk far beyond the period usually advised, with highly gratifying results."—*F. L. Wachenheim: Infant-Feeding; Its Principles and Practice, Lea & Febiger, Phila., 1915, p. 158.*

"Dextri-maltose has been substituted for lactose not infrequently, when the tolerance for the latter continues low."—*J. H. West: Low fat, high starch evaporated milk feeding for the marasmic baby, Arch. Pediat. 48:189-193, March, 1931.*

"Malt sugar is indicated when others fail to produce a sufficient gain, or when malassimilation of fat is evident."—*O. H. Wilson: The role of carbohydrates in infant feeding, Southern M. J. 11:177, March, 1918; abst. Arch. Pediat. 35:447, July, 1918.*

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